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THE MEDICAL AND PUBLIC HEALTH IMPORTANCE OF THE INSECTICIDE DDT

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I FEEL it a distinct honor to be invited to appear before this distinguished group of the medical profession and on this lectureship established to revere an outstanding physician. This appearance is regarded, not as a personal recognition of any particular contribution of mine, but as an acknowledgment of the part that entomology and entomologists can play and are playing in the important and expanding field of preventive medicine.

Perhaps this occasion is another evidence of the feeling that in this day of specialization the workers in a number of related fields must join hands in a coöperative effort to elucidate many disease problems and to apply the results of such research for the welfare of humanity.

Insect-borne diseases back through the ages have been a dominant factor in determining the fate of armies and the outcome of wars. It is therefore not surprising that forward-looking medical men and engi-

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neers of the Army and Navy gave early consideration to ways of meeting the need for more effective and practical means of combating these diseases and their insect carriers. The great progress that has been made during the last few years has been interpreted by many as resulting directly from the war. There is doubt in my mind, however, whether research is more productive under the pressure of war demands than in peace. Many of the recent advances in combating insects are prewar discoveries, or are based on knowledge gathered during peacetime, as in the case of insecticidal aerosols developed by Bureau of Entomology and Plant Quarantine workers, Sullivan, Goodhue, and Fales,[1] in 1940, and methyl bromide, developed largely as an agricultural fumigant a few years prior to the war.[2] True, war makes funds available and gives special purpose to research, provides a proving ground for its findings, and accelerates the development and utilization of discoveries.

Another force that is especially operative during war is that of education. This force is probably as virile and far reaching in preventive medicine as in any other field. The incidence of insect-borne diseases, with the serious efforts put forth by military authorities to control or prevent these diseases, has been a powerful educational influence. It has brought forcefully to the attention of our millions in the armed forces and their families the importance of these diseases and the preventive measures used against them. This broad interest aroused in preventive medicine surely should not be neglected in our further efforts in health education. This enlightenment has by no means been confined to the rank and file of the armies and to the nonprofessional men of civil life. It is more or less evident at higher levels in every branch of the military service. Many medical men in uniform have, perhaps for the first time, become aware of the magnitude and importance of preventive medicine and especially of medical entomological problems. Many medical schools have modified their curricula to include medical parasitology and other subjects of vital importance in preventive medicine. Even though it will be regarded by some of you as presumptuous on the part of a layman, I venture the statement that I sincerely trust these changes will persist, and that our medical profession as a whole will give increasing attention to disease prevention rather than to thinking largely in terms of disease cure.

Of course, disease prevention is an extremely broad and intricate matter involving nutrition, housing, transportation, general economic

conditions, and many fixed customs and habits, none of which are strictly medical. Responsibility in the field rests not alone on the medical profession, but involves many special groups and, in fact, the people as a whole. It is right and proper, however, that the medical profession and those working directly in preventive medicine should take aggressive leadership in research, organization, legislation, and education looking toward more rapid and general advancement of this field so vital to the people of the entire world.

Insects Important in Preventive Medicine

Insects and related arthropods rank high in importance to the health and prosperity of nations in both peace and war. Some of the world's most dreaded diseases, such as plague, epidemic typhus, and African sleeping sickness, are exclusively insect-borne. Likewise the world's most debilitating malady, malaria, is chargeable to insects. Then there is Rocky Mountain spotted fever, endemic typhus, scrub typhus, encephalomyelitis, yellow fever, dengue, relapsing fever, filariasis, kala azar, verruga, pappataci fever—a formidable array, for which insects, mites, and ticks are wholly responsible. Nor should we overlook the part played by insects in the carriage of many other diseases, such as dysentery, typhoid, and tularemia; the parasitic worms; and the trouble induced by direct attack of insects on man where no disease organism is directly involved, as in various forms of myiasis; stinging and biting pests; and those that burrow into the skin. Often worrisome forms of life, such as swarms of biting midges, mosquitoes, and fleas, may assume considerable importance in impairing efficiency and even health. The bothersome bedbug, the cockroach, the elusive flea, and the persistent chigger and seed tick, each receives its complement of profane epithets and exacts its toll of sleepless nights.

We are not inclined to associate with public health insects that carry or produce plant diseases; those that destroy vegetables or fruits, cereals, or sugarcane; or those that damage livestock or food products in storage. Yet they often are a dominant factor in decreasing food supplies, so that low-income groups, or even entire populations, suffer from malnutrition, and many die of starvation. Other effects of insects on human welfare, if not on health, are evident in the devastation of forests and grasslands, which increases the cost of suitable shelters and induces destructive soil erosion, floods, and forest fires. This by no means com-

pletes the picture, for insects feed upon our flowers and shrubs, gnaw holes in our draperies, rugs, and clothing, undermine our homes, feed upon our axe handles, and even interrupt communications by cutting down telegraph poles or burrowing through lead cables.

But insects are not all arch enemies of man. Of the some 620,000 species described, probably not more than 55,000 are recognized as being injurious. Thousands of species might be classed as neutral, and other thousands are beneficial. Some insects prey on our enemy species as parasites or predators; some contribute by destroying noxious weeds; some by breaking down dead plants and animals, so that they are returned to the soil to serve as plant food; some work over and aerate the soil; and others furnish dyes for the fine arts, fibers for clothing, or food for beneficial wildlife, our livestock and man.

In this last category the part that honeybees and other insects play in producing food often goes unrecognized. Thirty important food crops depend largely or solely upon insects to pollinate them. Without this assistance we would have to get along without such things as squash and other cucurbits, apples, sweet cherries, plums, and prunes. Furthermore, many of our crops so essential for livestock, soil improvement, and prevention of soil erosion would be barren or produce very little seed. This is true of alfalfa, the clovers, and others.

This theme is an extremely interesting and important one, and has a vital relationship to human welfare and therefore to any extensive efforts that man may put forth in combating disease-bearing and other insect enemies.

Insecticides Not the Only Weapons at Hand With Which to Fight Insects

The urge that everyone has to kill dangerous insects quickly and certainly, together with the publicity given to the insect-killing potentialities of the insecticide DDT, has diverted attention from the many other sound methods of combating insects. The enemy is so numerous, its modes of attack so diverse, and the danger of depending only on insecticides for control so grave that we must use every weapon at hand.

Only a few examples of the many ways of combating insects of medical importance other than by the use of insecticides are cited here. For mosquito control, drainage and other steps to eliminate breeding places are familiar examples. As is well known, elimination of manure

piles and accumulations of fermenting vegetable matter is far more important in combating houseflies and stableflies than the use of any sort of insecticide. Certain kinds of ticks can be controlled, or even eradicated, by the destruction or manipulation of their animal hosts.

Insecticides a Direct and Quick Weapon

In combating insect pests the use of insecticides has a strong popular appeal. We are loath to take action till the enemy is upon us, and by that time something drastic must be done. It is therefore fortunate that we have a number of dependable insecticides that may be called into play on short notice.

Our insecticide arsenal was badly affected by the war. Possible war needs for arsenic and demands for lead threatened for a time one of our major groups of weapons, the arsenicals. Copper demands depleted our supply of paris green and copper fungicides, shipping interference and adverse weather reduced supplies of vital military and household insecticides made from Kenya-grown pyrethrum flowers, and the Japanese soon took over Malaya and other oriental areas from which had come our major supply of derris, one of the plants from which the highly effective rotenone is derived. The reduction in pyrethrum combined with increased military demands was particularly trying because farmers had come to depend on this insecticide for controlling many pests of vegetable crops on which arsenicals and other materials dangerous to man could not be used safely. Furthermore, it left our householders and food handlers without ammunition in the spray gun, a device now found on almost every kitchen and store shelf. The Bureau of Entomology and Plant Quarantine and many other official and private groups not only put forth efforts to increase the culture of pyrethrum and rotenone-bearing plants on this hemisphere, but instituted a search for suitable substitutes for critical or scarce insecticides. Hundreds of synthetic organic compounds were tested against a number of insects. Some showed promise, but most compounds of this class have been found to be rather highly specific. Investigations were also pressed forward on synergists, i.e., materials that would accelerate or intensify the insect killing properties of compounds having insecticidal value. These investigations too have yielded worthwhile results. None of the materials or combinations studied, however, appear to equal the organic chemical, DDT as an all-round insecticide.

DDT an Outstanding Discovery

The common name DDT is based on the generic chemical name dichloro-diphenyl-trichloroethane, but more accurately designated by the long chemical name 1-trichloro-2, 2-bis (*p*-chlorophenyl) ethane (formerly called 2, 2-bis (*p*-chlorophenyl)-1, 1, 1-trichloroethane). This compound was first synthesized by a German student, Othmar Zeidler, in 1874.[3] Like thousands of other materials synthesized at universities, it remained on the shelves as just another compound until the Swiss firm of J. R. Geigy, A.-G., in its search for mothproofing agents tested many compounds and among them DDT, which displayed distinct insecticidal value. Wiesmann of the Swiss Agricultural Experiment Station, in coöperation with this firm showed it to have merit in combating certain agricultural pests[4] and in killing houseflies.[5] Late in 1942 a sample of the insecticide prepared by the Geigy Company, and called Gesarol Spray Insecticide, was sent by the Swiss firm to its American branch, which in turn submitted it to the United States Department of Agriculture for evaluation. A group of entomologists at the Orlando, Fla., laboratory of the Bureau of Entomology and Plant Quarantine, headed by E. F. Knipling, soon proved DDT to have a remarkable destructive effect on body lice. Research work conducted under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development was already well organized, and a colony of thousands of vigorous lice upon which to test various materials was already established; hence the development proceeded rapidly. In the meantime the Army had placed in the hands of men taking part in the North African campaign an effective louse-destroying agent known as MYL powder, which had been developed by the same scientists. DDT, where properly applied, was found to have remarkable persistence, and was not subject to deterioration as is the case with MYL powder, the principal constituent of which is pyrethrum. Furthermore, the grave problem presented by the shortage of pyrethrum appeared to have been solved.

Initial tests with DDT were conducted with caution, since the material appeared to be a nerve poison and it was suspected that possibly Germany had permitted the material to be shipped out of Switzerland in the hope that it might be used extensively on our troops and thus in some way adversely affect them. Extensive toxicological tests carried

out by the Food and Drug Administration and the National Institute of Health, however, failed to demonstrate any toxic effects from the use of a powder containing 10 per cent of DDT in the neutral carrier pyrophyllite. Accordingly, after rather extensive field trials involving civilians, troops, and prisoners, DDT powder was accepted for general military use against lice.

It was found that DDT used as a powder on the skin and garments would give protection against louse infestations for three weeks or longer. This material in the form of an emulsion could also be incorporated in the garments and fixed so firmly that it would not lose its insecticidal effect for periods as long as eight weeks even though the garments were washed at weekly intervals.

Extensive field trials of DDT were carried out by medical and sanitary officers in coöperation with the United States Typhus Commission, the Rockefeller Foundation, and local civilian agencies in North Africa. The difficulty of requiring people with various prejudices and religious beliefs to remove their clothing for treatment was met by the development of a simple dusting apparatus by which the powder could be introduced beneath the clothing.[6] The proof of the efficacy of DDT in controlling an epidemic of typhus was soon forthcoming. The stage was set in Naples for a devastating sweep of the disease through the civilian population, which would undoubtedly have involved our troops. The epic curbing of this outbreak has been recounted on previous occasions. The effective organization set-up and the availability of ample supplies of DDT, which was applied to more than a million and a quarter persons in a few months, can be credited with this amazing result.

Some indication of the wide interest in DDT is shown by the tremendous number of articles on the subject that have appeared in print in the last 2 or 3 years. A survey of the literature by R. C. Roark has shown that about 600 articles have been published.[7,8]

Chemistry and Manufacture of DDT

The original method of manufacturing DDT has been set forth briefly in a British patent assigned to J. R. Geigy, A.-G.[9]:

"225 parts of chlorobenzene are mixed with 147 parts of chloral or the corresponding amount of chloralhydrate and then 1000 parts of sulphuric acid monohydrate are added. Whilst stirring well the temperature rises to 60°C. and then sinks slowly down to room temperature,

the mass then containing solid parts. It is poured into a great deal of water, whereupon the product separates in solid form. It is well washed and crystallized from ethyl alcohol forming fine white crystals, having a weak fruit-like odour."

Results of early tests in this country with DDT were so promising that the chemical industry was encouraged to go into production as rapidly as possible, and every effort was put forth to make adequate supplies available to the military. The material was placed under allocation by the War Production Board on January 1, 1944 (Order No. M-340). However, as production was increased, new and more extended uses were found which continued to keep military demands ahead of production. At present about a dozen chemical firms are producing this insecticide and, with the exception of relatively small quantities that are devoted to research, the entire supply of approximately 2,000,000 pounds per month is going into military uses.

Technical DDT consists largely of the para-pará isomer of dichlorodiphenyltrichloroethane, which some of the ortho-pará isomer and ten of twelve other compounds. The para-pará isomer is the most highly insecticidal and constitutes about 70 per cent of the technical material, the ortho-pará isomer makes up about 25 per cent, and the other compounds the remaining 5 per cent. The refined or recrystallized product consists almost wholly of the para-para' isomer and is designed as pure DDT. This pure compound melts at 108.5° to 109°C. The technical product has a melting range of about 25°; therefore, specifications covering purchases for military uses designate a setting point rather than a melting point. It is set at not less than 88°C. A number of compounds containing DDT have been put out by commercial concerns under various trade names, such as Gesarol and Neocid.

DDT is practically insoluble in water, but dissolves readily in a number of organic solvents such as xylene, acetone, and chloroform. Petroleum oils also dissolve varying amounts of DDT; the less refined these oils are, the greater is their solvent power. Ordinary kerosene will dissolve approximately 5 per cent of DDT at room temperatures.

For general insecticidal uses there is no need to consider material of high purity and thus add to the cost of production. For special purposes, such as for incorporation in aerosol bombs, the use of refined DDT may be justified in order to minimize corrosive action on the containers.

The investigations in the Bureau of Entomology and Plant Quarantine of the chemical make-up of technical DDT have yielded important information.[10] Research chemists in the Bureau[11] have also developed a colorimetric method by which minute quantities of DDT can be determined which permits a more accurate evaluation of the residue problems such as on food and forage plants and in water.

Formulations of DDT

To get the highest insecticidal efficiency from any material it must be properly formulated to fit into the many conditions encountered. DDT has been prepared in various mixtures as dusts, sprays, and aerosols, but much remains to be done in this field. As has been stated, the simple mixture of finely ground DDT in pyrophyllite was first used in the field of medical entomology. Since that initial step, many formulations have been prepared for diverse uses against insects of medical, veterinary, and agricultural importance. These formulations involve numerous solvents, wetting agents, emulsifiers, and stickers, and various combinations including mixtures with other insecticides. Proper formulation of insecticides not only makes them more effective, but also ideally at least, more economical, more convenient to ship and store, more easily applied, and less likely to have an adverse effect on men, animals and plants.

Fortunately, for two of the major uses DDT can be very cheaply and easily prepared. I refer to the dust mixture already mentioned for louse control and to kerosene or fuel-oil solutions for use as a mosquito larvicide. Some difficulty has been experienced, however, with the DDT crystallizing out in the oil drums when the material is stored at low temperatures. Since these crystals are not easily redissolved, it is desirable to add an auxiliary solvent, such as xylene or a heavier petroleum fraction.

When the carriers employed in the sprays evaporate, beautiful crystals of DDT are left on the surface of sprayed objects. The type of these crystals varies much with the carrier used, as does also the rapidity with which they are formed. There is evidence that the type of crystalline deposit affects its insecticidal potency.

Methods of Application

Naturally, methods of applying insecticides must be governed by

the nature of the problem. The stability, solubility, residual effect, and other characteristics of DDT make possible the use of many different methods of application and have suggested almost innumerable types of apparatus for dispersing it. These range from the simple hand dusting, as in control of lice on man, to the application to jungle areas, by huge aircraft, of dusts, sprays, and aerosols for mosquito control. They also include impregnation of clothing and other fabrics in an emulsion or solution; the employment of explosives in various devices, of special generators to produce thermal aerosols, of manually-operated aerosol containers with liquefied gas as a propellent, of atomizers of diverse types and sizes (some little larger than a fountain pen), of various types of sprayers and dusters; and even the use of an oil can or a paint brush. Automatic drip cans or impregnated sawdust or other material have also been used for treating mosquito-breeding rice fields, streams, and ponds.

Most of these dispersal devices are in an experimental stage, and no doubt many new ones will be devised. It is a fertile field for those with inventive abilities. Through all the experimental and practical work the need has been apparent for special distributing equipment to meet the diverse conditions encountered in military operations and those more fully recognized here at home.

The development of methods for aerial application has been and still is of absorbing interest. Since 1922, when the Bureau of Entomology and Plant Quarantine first experimented with airplane dusting of calcium arsenate for control of the boll weevil on cotton, little attention has been devoted to spraying devices. The high toxicity of DDT to many insects gives us, for the first time, a liquid material that can be economically applied from the air. The Husman-Longcoy equipment for use on a Cub plane has proved useful and a basis for the development of other equipment, especially for employment on larger fast-flying craft. Tests have run the gamut from the Cub to large bombers and from tanks holding 35 gallons to those holding 500 or more. The helicopter, autogiro, and dirigible have not been forgotten. Prior to this work little information was available upon which to base even a guess on the effect of speed, type of plane, place and character of discharge, and other factors influencing the break-up of liquids. Droplet size is a highly important item in insecticidal efficiency which we must watch.

Toxicology

One of the first points considered in connection with the development of a new insecticide is its toxicity to man and higher animals, as well as to various lower forms of life beneficial to man. Therefore, as soon as the marked insecticidal value of DDT was determined at the Orlando laboratory, steps were taken to have its toxicological effect investigated by Dr. Herbert O. Calvery and his associates in the Food and Drug Administration and Dr. Paul A. Neal, of the National Institute of Health. Later, Dr. Robert A. Kehoe, of the Kettering Institute of the University of Cincinnati, and Dr. M. I. Smith, of the National Institute of Health, undertook supplementary work.

Some of the results of this excellent research have been published,[12-16] and no attempt will be made here to review them in detail. There is complete agreement among these workers that DDT acts as a nerve poison when ingested or absorbed, that its toxicity to different warm-blooded animals varies widely, but that its acute toxicity orally is not of a high order. For instance, the oral LD 50 (median lethal dose) for white rats ranges from 200 to 300 mg. per kilogram of body weight, depending on size and age; for rabbits about 500; for dogs about 200; and for mice about 400. In preliminary experiments carried out by Orr and Mott,[17] horses and sheep showed no clinical evidence of poisoning when given DDT by mouth in doses of 100 to 200 mg. per kilogram repeated for several days. Sheep were given ½ to 2 grams per kilogram of body weight as a single dose. The largest dose caused tremors for one day and loss of appetite for two or three days. Some cows showed tremors after the first feeding of 100 mg. per kilogram but recovered even when the dose was increased after a week to 150 mg. and after another week to 200 mg. Some of these animals when posted showed hemorrhagic spots on the heart and other viscera. These spots apparently disappear after a few weeks. It is characteristic of DDT poisoning that animals may develop tremors from daily doses, but that these may entirely clear up while the administration is being continued at the same level.

It was determined early by Dr. Calvery that no toxicity or irritation results from 10 per cent of DDT in pyrophyllite applied as a dust to the skin. This has been amply demonstrated by the free use of the powder by hundreds of thousands of troops and civilians in louse con-

trol. DDT in solution, however, can be absorbed through the skin. This is particularly true of oil solutions. There was some fear that DDT solutions might prove toxic when used as sprays, and especially as aerosols but extensive tests by the National Institute of Health showed that animals exposed to very heavy doses in strengths adequate to kill insects produced no ill effects if the animals were not allowed to lick the insecticides from their bodies.

Preliminary experiments indicate that DDT is rather poisonous to poultry and birds. Investigations being conducted by the Fish and Wildlife Service indicate that birds are more tolerant of DDT than mammals and that wild duck are especially resistant, but that snakes, salamanders, toads, and frogs may be killed by dosages in the upper range of insecticidal efficiency. Unfortunately, fish are markedly susceptible. This appears to be especially true of trout, and it is possible that they may be injured by feeding on insects dropping into the water after being killed by DDT. Apparently DDT is most toxic to fish when applied in colloidal suspension in water, with emulsion next, and surface applications of dusts and oil solutions least poisonous to them.

The chronic toxicity of DDT in various forms has not been fully evaluated; although relatively large daily doses can be tolerated over long periods, there is evidence of some cumulative effect and of slight sensitization in animals but not in man.

It may be concluded from available facts that DDT is much less dangerous to man and higher animals from direct toxic action than are many other insecticides, but it should be handled with care, especially to avoid ingestion and prolonged contact of oil solutions with the skin.

Among the insects there is a wide range of susceptibility. DDT kills both by contact and as a stomach poison. Some insects, such as the Mexican bean beetle and boll weevil are little affected by it when applied in practical doses. On the other hand, extremely minute quantities picked up by flies crawling over a surface sprayed months before will effect a kill, and as little as 1 part of DDT to 100 million parts of water will destroy certain mosquito larvae in the laboratory. Recent work by the Bureau of Entomology and Plant Quarantine indicate that 1 gamma (one-millionth of a gram) will kill a housefly.

Part Played by DDT in the War

There have been in circulation so many statements about DDT

and its insect-killing powers that it is logical to ask—just what is DDT doing toward winning the war? It seems unnecessary to dwell on the importance of insects as annoyers and disease carriers in large-scale military operations. History is replete with evidence of this. Napoleon's operations in the West Indies were definitely stopped and the whole history of that area, and perhaps of the United States, was changed by the yellow-fever mosquito, which killed more than three-fourths of his army. Louse-borne typhus and malaria have determined the outcome of many campaigns; likewise, fly-carried dysentery and typhoid have seriously interfered with many military operations and caused much suffering, as happened in our Spanish-American War.

The world-wide struggle in which we are now engaged has given opportunity for every insect-transmitted malady to attack naturally non-immune groups of men. Furthermore, fast transport, especially by air, makes possible the movement in a few hours of infected personnel and infected insects from continent to continent and from hemisphere to hemisphere. To cope with this situation the best entomological and chemical knowledge, the soundest medical judgment, and the highest engineering skill are demanded. The promptness with which threatening outbreaks have been quelled and the present low incidence of these diseases among our vast armies speak for the effectiveness with which these forces have been brought to bear on disease problems.

The success of the campaign against the typhus outbreak in Naples during the winter of 1943-44 was due almost wholly to this new insecticide. It would not be fair, however, to ascribe to DDT more than its rightful share of the credit for these remarkable results. Recognition must be given also to the highly effective organization and vigorous and persistent efforts of the Typhus Commission, the Medical Corps of the Army, the Public Health Service, the Rockefeller Foundation, and other agencies concerned. Nor should we forget the quiet, indefatigable researchers of the Orlando laboratory of the Bureau of Entomology and Plant Quarantine, who made this effective weapon ready for just such an emergency. Obviously, without a sound organization, appropriate educational work, and full coöperation, including that of line officers and the entire military personnel, it would have been impossible to set up delousing stations, each capable of treating 5,000 persons a day, and to round up from their underground habitations and delouse the families of Italians. More than a million and a quarter persons were treated dur-

ing that winter, and owing to the louse powder, supplemented with methyl bromide fumigation, practically no cases of typhus have occurred among our forces. The introduction into this country of lice and louse-borne diseases with prisoners of war, refugees, and returning troops, has also been prevented. The armies of Great Britain are also making use of DDT against lice, both as a powder and as a clothing impregnant.

Mosquito control is a major factor in the prevention of malaria, dengue, filariasis, encephalitis, and yellow fever, and DDT is coming to play a major role in combating these diseases in our war operations. True, drugs are of recognized value in suppressing and treating malaria, but no drug has yet been found that is a true preventive or a dependable cure. For yellow fever we have a preventive vaccine that gives our troops protection, but there are multitudes of susceptible people, both in this country and in other parts of the world, who are not vaccinated, and we must depend upon fighting mosquito carriers, especially on aircraft and around airports, if we are to hold this dread disease at its present insignificant level. As for the other diseases mentioned, there is no known method of prevention other than through mosquito control.

Thus far DDT has been employed in only a minor way in the anti-mosquito work of the military, and not at all by civilians. It is commencing to strengthen our aggressive war on mosquito breeding in training centers in this country and in camps in stabilized areas. Its greatest usefulness, however, is in ridding beachheads of infected mosquitoes—in fact, all mosquitoes—at the critical landing period when head and bed nets and other mechanical protection cannot be used and usual antilarval measures cannot be employed. It seems almost incredible that on D-day a few sweeps of a fleet of bombers with an almost invisible discharge of DDT in oil can destroy practically every mosquito in the area and permit our forces to concentrate on the Japs without danger of malaria or dengue infections for at least several days.

As little as 1/10 pound of DDT per acre has been shown by the entomologists at Orlando to kill all larvae of the common malaria mosquito, *Anopheles quadrimaculatus* Say, under favorable field conditions. An application of 1 quart of oil containing 5 per cent of DDT to the acre, under ordinary conditions of vegetation, will kill all larvae of this species. Even under jungle conditions 3 quarts of this solution per acre, if broken into fine spray particles 20 to 200 microns in diameter, will kill more than 95 per cent of all mosquitoes, both larvae and adults in

the area. Dusts containing 10 per cent of DDT used at the rate of 1 to 2 pounds per acre gave a complete kill and reduced breeding for one to two weeks in moderate vegetation and longer in heavy vegetation. Wind and wave action soon terminate the residual killing effect of both dusts and oil solutions. In xylene emulsions DDT can be prepared and shipped in concentrated form and diluted with water as used. Such emulsions were effective against *Anopheles* and several species of culicine larvae in dilutions as low as 1 part to 20 million. As little as 1 part per million had a lasting larvicidal effect in rain barrels.

As yet DDT has not been employed in insecticidal aerosols in field operations. However, experimental work carried out by the Bureau of Entomology and Plant Quarantine both at Orlando and at the Beltsville Research Center, has shown that the addition of 3 per cent of DDT materially increases the effectiveness of the pyrethrum aerosol at the strength now used against mosquitoes, and against flies its killing power is greatly enhanced.

One of the most remarkable qualities of DDT as an insecticide is its persistence or residual effect. This characteristic may be the one that will give us the whip hand in malaria control. When DDT in solution or emulsion is applied to wood or canvas as a medium fine spray at the rate of 200 mg. per square foot of surface, mosquitoes resting on such surfaces are killed in a few hours. This killing effect persists for several months. Its persistence is even more striking in the case of flies. It is possible to spray fences, buildings, and even vegetation around fly breeding places, and expect the flies to be killed as they emerge from their puparia and crawl upon such objects. The insects are excited after they have rested on treated surfaces for a short time, but even though they may fly away most of them succumb. Most mosquitoes normally rest on nearby objects for at least a short time after becoming engorged with blood. Some fly about and alight several times while they are seeking a blood meal. In sprayed rooms or tents this would appear to insure contact of the insects with the DDT crystals and resultant death before the completion of development within their bodies and introduction into susceptible hosts of the organisms of malaria, yellow fever, dengue, or filariasis.

The fly problem has been acute in a number of the war theatres. This was particularly true in North Africa and on some of the islands of the central and southwest Pacific. In the African operations house-

flies were mainly involved. In the Pacific blowflies have been most troublesome. Unfortunately, DDT was not available during the North African campaign, but it is now meeting an urgent need in the Pacific theatre. DDT sprayed from the air has done much to remove the hazards of fly-borne dysentery and annoyance from flies during landing operations. Applications from the air, supplemented by the spraying of tents, buildings, latrines, and equipment, and by the usual sanitary and other fly-control procedures, hold the fly population to a minimum.

The residual effect of DDT is particularly useful in combating flies. This was first brought out by Wiesmann's work in Switzerland.[5] Concurrent work by the Bureau of Entomology and Plant Quarantine in this country,[18,19] showed that 5 per cent of DDT in kerosene applied to wood surfaces in buildings would remain highly toxic to houseflies for four to six months, and that aqueous emulsions were equally effective. The type of surface, the presence of oils or grease and dust in the air, and other factors influence the duration of effectiveness. Incorporation of DDT in paints and varnishes holds little promise, but the material retains considerable killing power when applied in cold-water paints.

The excreta of animals to which DDT has been fed kills flies crawling over it and prevents maggot growth. DDT has also shown some possibilities for treating manure to prevent fly breeding.

DDT is remarkably effective against fleas, either on animal hosts or on the soil or floors upon which they develop. This effectiveness has been shown for the common cat and dog fleas, the Indian rat flea, the sticktight flea, and others. Some preliminary tests indicate that fleas on rats can be destroyed by spraying or dusting the rat runs with DDT formulations.

Although bedbugs are of little importance in disease transmission, their indirect effect on human efficiency through annoyance and loss of sleep is recognized. The effectiveness of DDT against these disgusting pests is almost unbelievable. A 5 per cent solution of DDT in refined kerosene, applied as a spray to infested beds and mattresses, not only kills the bugs actually struck but also persists for six or eight months so that any bugs coming in contact with the sprayed surfaces are killed.[20]

Another group of insects that play a small part in disease distribution are the cockroaches. The action of DDT against these pests is not so

spectacular, but it is distinctly toxic to them. Work thus far indicates, however, that the standard sodium fluoride treatment or pyrethrum as a contact spray is more effective.

Ticks, almost down to the last species, may be considered potential disease carriers. Several species are especially to be condemned, since they carry such deadly diseases as Rocky Mountain spotted fever, tularemia, and relapsing fever, produce paralytic conditions, and in many instances sorely annoy and cause secondary infection through their irritating bites. In experimental work carried out by Gouck and Smith[21] 5 per cent of DDT in aqueous emulsions was effective against various stages of the brown dog tick and larvae of the lone star tick on dogs, and emulsions containing 0.5 per cent of DDT sprayed on infested roadside vegetation gave a high degree of control of adults of the black-legged tick for at least three weeks.

Preliminary experiments with DDT in kerosene or fuel oil applied as a spray to areas infested with the sand fly (*Culicoides*) and the black-fly appeared to eliminate the adults for at least a few days. Such solutions painted on window screens also prevented the sand flies from entering.

Chiggers and other mites claim our attention by their transmission of scrub typhus and by the extreme itching of their toxic bites. Numerous fever and other systemic reactions occur, and severe secondary infections are frequent. DDT promises to be valuable in combating these pests.

What Does the Future Hold?

Peacetime developments have been adapted quickly to war needs, and we must be as alert in turning the implements of war to postwar problems. Fortunately, in the field of clinical medicine practically all the equipment, drugs, and surgical techniques that are emanating from the war effort can be applied at once in peace time. This is almost as true in preventive medicine, though the adaptation may come more slowly.

Since the interest of both physicians and laymen in preventive medicine is now far more general than before the war, can we not grasp this opportunity to extend research in the causation and prevention of disease and to further the application of acquired knowledge in this field?

Are we as physicians, sanitarians, engineers, entomologists, and economists to be content with the dynamite of plague hidden in our western yard, with the presence in our South of myriads of pestiferous yellow-fever mosquitoes ready to scatter the dread black vomit and the pain of breakbone fever over our land? Are we to continue to condone the presence of millions of rats in our cities and villages, and on our farms, permitting them to harvest the fruits of our labor and, with their associates the fleas and mites, to debilitate our people with endemic typhus? How long are we to harbor among the poor, and too often among the affluent as well, the disgusting louse? We know that these parasites have brought death to millions, that they attack man exclusively, and that they cannot survive without our blood and the warmth of our bodies. We now know also that a single treatment of every infested person with DDT would eliminate these lice from the earth. Should we be content to look on complaisantly while emaciated millions drag their malaria-shackled bodies from neglected fields to tottering huts? These problems are a challenge to the world that must be accepted. I do not mean to depreciate the excellent work that has been done, but the urge is on us and in the immediate postwar period it would seem both desirable and necessary to quicken our efforts.

After the fall of Germany and Japan we will still be confronted with armies of dangerous insect enemies which in the long run may cause more suffering and death and economic losses than our present human foes. In this war on the insects DDT will, I am confident, occupy a leading place in the arsenal we must keep ever ready to meet their varied forms and diverse methods of attack.

Modern transportation makes all countries of the world close neighbors. Therefore, one of our first and continuing problems is to prevent the spread of dangerous insects and the diseases they carry. In this field DDT and pyrethrum aerosols and sprays, if properly applied in aircraft, ships, and trains, will do much to minimize this hazard. The insect-control work around hospitals housing returned veterans, as well as educational work, should go far in preventing any serious outbreaks of insect-borne diseases. The extended antimalaria program proposed by the United States Public Health Service in coöperation with State health authorities should further aid in preventing the introduction and spread of mosquito-carried maladies. It would also be taking the first long step toward that ambitious program suggested by Dr. L. L. Wil-

liams, Jr. of eradicating malaria from this country. In this program DDT, especially in the form of a residual spray, will be a major weapon.

It is difficult to foresee the precise place that DDT may assume in the future. In addition to the fields of application briefly mentioned above, one can visualize farms with contented livestock and cleaner dairy products through the use of DDT against hornflies, stableflies, and houseflies; also outing areas with less annoyance from punkies or sand flies (*Culicoides*), blackflies, and mosquitoes. Insect destroyers of crops may be held in stricter control, thus helping to assure ample and economic food production which in turn means better general health and happiness.

DDT appears destined to assume an important role in controlling sand flies (*Phlebotomus*) and thus reducing the incidence of kala azar and sand fly fever. Likewise, through its use against these insects, the dread disease verruga may be controlled in Peru and Colombia. Tick control will probably be materially accelerated by the use of DDT, and this material will doubtless find an expanded field of usefulness in combating flies of all kinds. The Chagas disease situation in the Americas may be materially helped by the availability of DDT in postwar days and its employment against the kissing bugs that transmit that malady. The persistence of this insecticide on vegetation suggests the possibility of its successful use against the dread sleeping sickness of Africa, as well as the persistent and infection-carrying eye gnats in various parts of the world. This would mean a great boon to the peoples in many lands where chronic conjunctivitis, trachoma, and resulting blindness are so prevalent.

Due regard must be had for the detrimental effect of DDT on beneficial insects and other forms of life when its widespread application is contemplated. We must learn more about the general field of usefulness of DDT as an insecticide, and especially about its limitations. Much remains to be done in the perfecting of formulas for diverse uses and methods and equipment for application.

General James S. Simmons, of the Surgeon General's Office, United States Army, has summed up his views on DDT as follows: "I feel quite sure that the knowledge gained of this amazing chemical, constitutes the most valuable single contribution of our wartime medical research to the future health and welfare, not only of this nation, but of the world."[22] Magic insect killer though DDT is, it must be applied

by the right method, in the right form, and at the right time. Many writers have claimed too much for DDT. It is not a panacea for all insect ills, but it should hold an important place in the preventive medicine of the future.

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CLINICAL OBSERVATIONS ON THE TREATMENT OF VARIOUS INFECTIONS WITH PENICILLIN*

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THE purpose of this paper is to review some of the significant changes that penicillin therapy has brought about in the prognosis, course, and management of certain infections. Of necessity the discussion of the various diseases that I shall consider will be incomplete since an entire article could well be devoted to any one of them. An attempt will, however, be made to illustrate the more important features of penicillin therapy in pneumococcic meningitis, acute and chronic osteomyelitis, and acute bacterial endocarditis.

The material presented herein is based on the observation of cases treated at the Evans Memorial Hospital during the last three years under the direction of Dr. Chester S. Keefer, and on a study of the case reports submitted by various investigators to Dr. Keefer in his capacity as chairman of the Committee on Chemotherapeutics and Other Agents of the National Research Council.

PNEUMOCOCCIC MENINGITIS

The seriousness of pneumococcic meningitis is well known, for prior to the introduction of the sulfonamides its mortality was almost 100 per cent. With sulfonamide therapy the reported mortality rates have varied for the most part between 60 and 80 per cent, although better results have occasionally been obtained in small, selected groups of patients. It is well known that several factors influence the prognosis in this disease. Thus, the mortality rate is highest in patients under two and over sixty years of age. It is also higher in those cases in which

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From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

meningitis follows pneumonia than in those in which it follows infections of the middle ear or paranasal sinuses, or in which no primary focus can be demonstrated.

The mortality rate in more than 400 cases treated with penicillin that have been reported to the Committee on Chemotherapeutics and Other Agents is approximately 50 per cent. No difference could be demonstrated in the gross mortality rates between the patients treated with penicillin alone and those treated with a combination of penicillin and a sulfonamide. Until these cases can be more completely analyzed, however, this finding should not be considered as conclusive, since the results in smaller series of cases reported by Waring and Smith,[1] by Sweet and his associates[2] and by Brigadier Cairns strongly suggest that combined therapy is much more effective than treatment with either agent alone.

In their response to treatment, the patients with pneumococcic meningitis fell into four main categories. In the first group were patients who had fulminating infections or were treated late in the course of the disease. They were usually in deep coma and were obviously moribund when treatment was started. Heroic measures were ineffective, and death occurred in forty-eight hours or less despite the use of large doses of penicillin, sulfonamides, and in several instances type-specific antiserum as well. An example of the failure of intensive therapy to alter the course of a fulminating infection, is illustrated by the first case.

Case 1. C. F., a 59-year old man, was making a satisfactory recovery from an attack of lobar pneumonia when eighteen hours before entry he developed a severe headache and shortly thereafter became comatose. On admission to the hospital the blood culture contained 42,000 colonies of Type VIII pneumococcus per cubic centimeter, and a culture of the spinal fluid, which was grossly purulent, revealed 100,000,000 organisms per cubic centimeter. Therapy was instituted within less than 1 hour after the patient reached the hospital; 20,000 units of penicillin was injected intrathecally through the lumbar sac and the same amount was given intramuscularly every three hours. Two and five tenth grams of sodium sulfamerazine was injected intravenously shortly after penicillin therapy was started. Twelve hours later a second lumbar puncture was performed and another 20,000 units of penicillin was administered intrathecally. An hour later after appropriate tests had

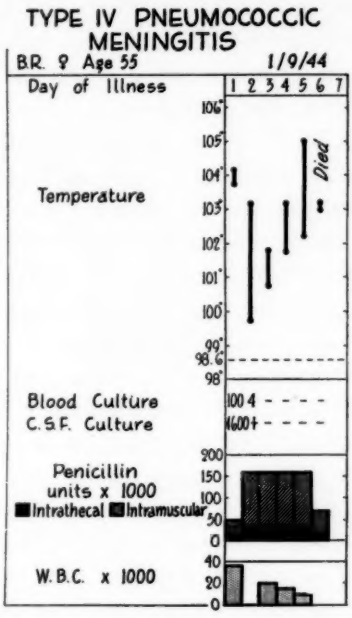

Fig. 1 (Case 2).—Clinical course of a patient with pneumococcic meningitis who showed temporary improvement after the administration of penicillin. Cultures of the blood and spinal fluid became sterile but the patient died on the sixth day of the illness.

revealed no evidence of sensitivity the patient was given 100,000 units of Type VIII pneumococcus rabbit antiserum intravenously. None of these measures effected any improvement, and the patient died seventeen hours after treatment was started, thirty-six hours after the first appearance of the symptoms of meningitis.

The patients in the second group were also desperately sick and usually comatose, but during the first twenty-four to forty-eight hours of treatment some evidence of improvement could often be detected. Frequently the temperature became lower, and at the same time the organisms either disappeared from the blood and spinal fluid or were markedly reduced in number. After a brief period of apparent improvement, these patients rapidly deteriorated and died within sixty to one hundred and twenty hours after the beginning of treatment. At autopsy culture of the meningeal exudate was often sterile, and when positive cultures were obtained, the number of organisms found was usually insignificant. It has been believed that in these cases in which

the infection was obviously coming under control, death must be attributed to toxemia, or more specifically to damage inflicted on the central nervous system while the infection was still active. The second case is illustrative of this type of response.

Case 2. (Fig. 1.) B. R., a 55-year-old woman, had had an acute otitis media and was admitted to the hospital five hours after she had developed a stiff neck. She was comatose at the time of admission, and treatment with penicillin was started within less than 1 hour. As indicated in the chart, the temperature fell and cultures of the blood and spinal fluid became negative twenty-four hours later. The patient remained comatose, however, and the temperature again rose. Consciousness was not regained, and 24 hours before death peripheral vascular collapse developed and persisted despite treatment with oxygen, plasma, and other ressuscitative measures. Post mortem examination showed an abscess in the right parietal lobe and a layer of fibrinous exudate over the whole convexity of the brain. Cultures of the abscess, of the exudate, and of the ventricular fluid were sterile.

The third group of patients included those in whom continuing improvement could be demonstrated within a short time after the beginning of treatment and who progressed to an uncomplicated recovery. These patients were treated fairly early and were in much more favorable condition at the beginning of treatment than those in the first two groups. It was not unusual for the cultures of the blood and spinal fluid in such cases to become negative within twenty-four to forty-eight hours, and while further improvement was often slow, it was usually possible to predict at the end of four to six days that the patient would recover. The next case is that of a patient who made an uncomplicated recovery on combined penicillin and sulfamerazine therapy.

Case 3. (Fig. 2). S. B., a 37-year-old woman, was recovering from a mild upper-respiratory infection when twenty-two hours before admission she was awakened from a sound sleep with headache, nausea, and vomiting. Stiffness of the neck was first observed a few hours before entry.

On admission the patient was conscious but confused and restless. No source of the infection could be demonstrated. After eleven hours of treatment with sulfamerazine she became comatose, and therapy with penicillin was instituted as indicated in the chart. At this time

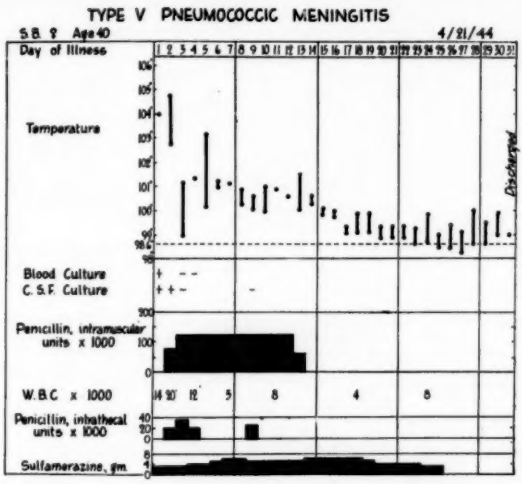

Fig. 2 (Case 3).—Chart showing progressive improvement and ultimate recovery in a patient with pneumococcic meningitis who was treated with penicillin and sulfamerazine. The development of a complete spinal subarachnoid block on the fourth day of treatment was not accompanied by a relapse of the infection, presumably because of the effective antibacterial action of sulfamerazine.

culture of the cerebrospinal fluid showed two hundred and fifty organisms per cubic centimeter. Within 24 hours after penicillin was started the patient was conscious and rational, although her responses were slow. On the evening of the fourth day and for the next five days no fluid could be obtained by lumbar puncture. In view of the favorable course intrathecal therapy was discontinued. After thirteen days of treatment the patient was clinically well except for slight rigidity of the neck and the persistence of a low-grade fever. The penicillin was stopped but sulfamerazine was continued for another two weeks. The patient recovered without sequelae and has remained well.

The fourth group was comprised of patients who while apparently making satisfactory progress either relapsed or developed complications. Relapses occasionally occurred early, and were usually due to the development of a subarachnoid block that prevented the diffusion of penicillin throughout the subarachnoid space. This complication is illustrated by the next case.

Case 4. (Fig. 3.) H. L., a 79-year-old man, developed a headache

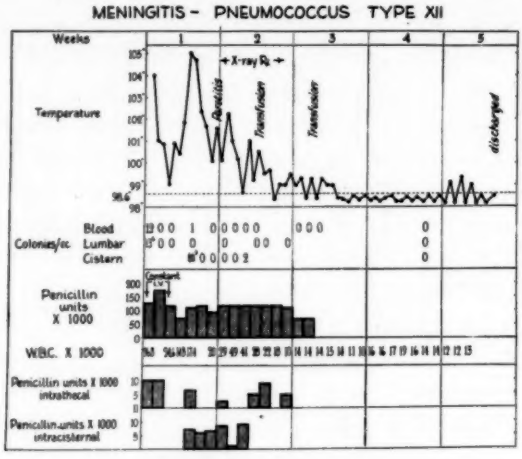

Fig. 3 (Case 4).—Clinical course of a 79-year-old man with pneumococcic meningitis who was treated with penicillin alone. Relapse occurred on the fifth day of treatment following the development of a complete spinal subarachnoid block. The infection was again controlled when penicillin was injected into the cisterna magna and the patient progressed to a complete recovery.

and stiff neck, and treatment was started eighteen hours later. We were unable to discover the primary focus of the infection. On systemic and intrathecal penicillin the patient's progress was satisfactory until the third day, when the signs of a complete spinal subarachnoid block developed. Intrathecal penicillin was then discontinued until the fifth day, when a sharp rise in the temperature occurred and the patient became comatose. Penicillin was then introduced daily into the cisterna magna for a period of seven days, at the end of which time the block had disappeared and intrathecal administration by the lumbar route was resumed. The patient eventually made a complete recovery and has been well and working for two years.

As suggested by the experience with the previous case, the incidence of relapses resulting from the development of a spinal subarachnoid block may be decreased by administering one of the sulfonamides in addition to penicillin.

Relapses that occurred after treatment had either been discontinued or when the intensity of the treatment was being gradually relaxed were more frequent than those that appeared early in the

course of treatment. The fact that pneumococcic meningitis is prone to relapse is well known, and many cases have been reported in which the patient suffered multiple relapses over the course of many weeks or months. In patients who relapse, attempts to demonstrate an extrameningeal source of the reinfection are usually fruitless. It is our belief that in such cases viable bacteria persist in the meninges, presumably in areas where plastic exudate is present. We have arrived at the conclusion that, unless an extrameningeal focus can be clearly implicated, continued intensive treatment of the meningitis is a more rational course than a blind surgical attack on the mastoids or paranasal sinuses. This view has also been expressed by Brigadier Cairns, who in a recent lecture on the treatment of pneumococcic meningitis with penicillin presented several excellent photographs of pathologic specimens demonstrating small foci of persisting intrameningeal infection that could well serve as the source for a reinvasion of the entire subarachnoid space.

No data are available at present on which to base any estimate as to how many patients who recover from pneumococcic meningitis show residual damage to the central nervous system. This sequela has been reported both in adults and in infants and children. In the latter group the damage may not be apparent until sufficient time has elapsed to indicate that mental development is not progressing normally.

The question as to what constitutes adequate penicillin therapy in pneumococcic meningitis needs further study. Actually, each case presents individual problems, so that hard and fast rules cannot be laid down. For most adults, the injection of 10,000 to 20,000 units intrathecally every twelve hours and the systemic administration of 100,000 to 200,000 units a day appear to be sufficient dosage to control the infection. The concomitant administration of sulfadiazine or sulfamerazine in doses sufficient to maintain a blood level of free drug of 10 to 15 mg. per 100 cubic centimeters also appears advisable.

More difficult to decide is the problem of how long to continue treatment. Both the clinical condition of the patient and the spinal-fluid findings may be misleading. Relapses may occur after the temperature has remained normal for a week or more, after repeated sterile cultures of the spinal fluid have been obtained, after the spinal-fluid cell count has returned practically to normal, and after the spinal-fluid sugar has remained well within normal limits for several

days. Because of the uncertainty as to when these patients are actually cured, we continue penicillin therapy for at least one week after apparent complete recovery and administer a sulfonamide for an additional two or more weeks.

When the primary focus in pneumococcic meningitis is located in the middle ear or paranasal sinuses, the question of the surgical treatment of such a focus usually comes up for consideration. The opinion most widely held at present is that the early surgical treatment of such foci has little effect on the course of the meningitis. Energetic therapy of the meningeal infection in the majority of cases will also control the infection at the portal of entry. In a few cases in which there is evidence of continuing infection at the primary site after the meningitis has been brought under control, surgical treatment of such areas can then be undertaken.

Acute Hematogenous Osteomyelitis

In acute hematogenous osteomyelitis the beneficial effects of penicillin on both the systemic infection and the local lesions of the bone and soft tissues has been repeatedly demonstrated. Of the cases of acute hematogenous osteomyelitis treated with penicillin that have been reported to the Committee on Chemotherapeutics and Other Agents, recovery from the systemic illness has taken place in 95 per cent. All these patients were seriously ill, almost half of them having staphylococcic bacteremia at the time treatment was begun. It has been a common observation that in severe staphylococcic infections treated with penicillin toxicity frequently abates several days before the temperature returns to normal. The usual course of events in acute osteomyelitis treated with penicillin has been for the patients to show marked improvement in their general condition, characterized by a return of appetite and a disappearance of lethargy and irritability within forty-eight to ninety-six hours. The temperature may return to normal during this time, but more frequently it remains somewhat elevated for seven to ten days. By the time it returns to normal, many patients appear to have recovered entirely from the systemic infection. In a few cases with multiple metastatic foci, improvement has been slower and the patients have remained acutely ill for one to two weeks.

With regard to the fate of the local lesion, information as to how many of these patients have recovered without the development of foci

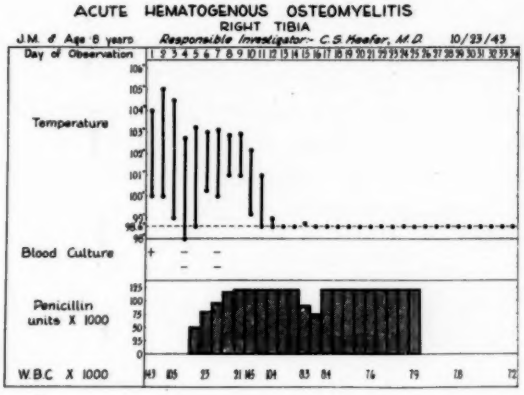

Fig. 4 (Case 5).—Clinical course of an 8-year-old boy with acute hematogenous osteomyelitis of the tibia treated with penicillin alone without surgical intervention. The patient recovered completely and has remained well for 18 months without developing any signs of sequestration.

of chronic infection in the bone is not yet available. In the cases that we have observed the response of the local lesion has often been striking. In those that have been treated early, before a soft-tissue abscess has formed, the signs of acute inflammation have receded progressively, so that as a rule the affected part has appeared normal or nearly so after ten to twenty days of treatment. In the cases in which there has been progressive improvement, we have not believed that surgical intervention was necessary. On the contrary, we have been impressed with the fact that these patients recover more rapidly and more completely if surgery is withheld. Only rarely do they develop sequestra or draining sinuses that require later surgical treatment.

Case 5. (Fig. 4.) J. M., an 8-year-old boy, developed symptoms of acute osteomyelitis of the tibia three days before entry to the hospital. Four days of sulfathiazole therapy resulted in a clearing of bacteria from the blood stream, but the patient remained acutely ill and the local signs of inflammation were advancing. Although the temperature did not return to normal until eight days after the beginning of penicillin treatment, the patient's general condition was markedly improved within seventy-two hours, and during the same time there was distinct lessening of the local signs of acute inflammation. Pain and tenderness were almost entirely gone by the end of one week, although

some swelling of the leg persisted until two days before treatment was discontinued. The patient has been followed for 1½ years without developing any signs of sequestration or of a recurrence.

Even in patients who have been treated late—that is, after the infection has been present for a week or more—it has often been possible to obtain satisfactory resolution of the local process without resorting to surgery. In cases that have developed a definite abscess, if intensive penicillin therapy does not effect prompt improvement, it is desirable to evacuate the abscess and release pus from the intramedullary cavity through multiple drill holes. Recovery in these cases has been hastened by closing the incision by primary suture after placing one or more soft-rubber catheters in the wound for the local instillation of penicillin postoperatively. These catheters are clamped after penicillin is injected and do not act as drains.

In cases of acute osteomyelitis in which a suppurative arthritis exists, systemic treatment must be supported by intra-articular injections of penicillin if serious damage to the joint is to be prevented.

With regard to dosage, in acutely ill patients we now administer 25,000 units intramuscularly every two to three hours (200,000 to 300,000 a day) until the infection is well under control. After ten days to two weeks, if progress has been satisfactory, the three-hourly dose is reduced to 15,000 units. We believe that treatment should be continued for a week to ten days after the temperature has become normal and the signs of local inflammation have entirely subsided. This usually means a minimum of three weeks of treatment; in severe cases even more prolonged therapy may be necessary.

Judgment as to when to stop treatment must be made on purely clinical grounds, since the roentgenographic changes in the bone do not keep pace with the clinical course. Frequently destruction of bone appears to be greatest at a time when it is obvious clinically that the patient has recovered. This situation is illustrated in Fig. 5, in which are shown three views of the femur in a child two years old. Treatment was begun about three days after the appearance of symptoms, and for the next twenty-four days the patient received 10,000 units of penicillin intramuscularly every three hours. The view on the left is that taken at the beginning of treatment, that in the center was taken just as treatment was being completed, and the one on the right was taken six weeks later.

A B C

Fig. 5.—Roentgenograms of the right femur of a 2-year-old girl with acute osteomyelitis. The patient received penicillin for 24 days. No operation was performed. 5A.—Roentgenogram taken at the beginning of treatment. 5B.—Roentgenogram taken the day treatment was completed. Although roentgenographic evidence of bone damage was greatest at this time, clinically the patient had completely recovered from both the systemic and local infection. 5C —Roentgenogram taken 6 weeks after the completion of treatment illustrating the rapid repair of bone in the absence of further treatment after the infection had been controlled.

On the basis of the experience to date, it seems safe to predict that with the use of penicillin acute hematogenous osteomyelitis will be regarded more and more as primarily a medical disease, although certain cases will still require careful surgical management of the local lesion.

Chronic Osteomyelitis

Chronic osteomyelitis, on the other hand, must still be considered largely a surgical problem. In occasional patients the use of penicillin alone may result in a prolonged remission, but in the majority of cases experience has indicated that the combined use of penicillin and surgery is necessary to achieve the best results.[3] The reasons for this are easily understood. Penicillin diffusing from the blood stream, or, after local application, from thick-walled sinus tracts frequently fails to reach bacteria that are present in scar tissue and sequestra, with the result either that healing does not take place or that if it does, viable

bacteria remain in the tissues and reactivate the infection within a short time.

Without going into details, I should like to outline the program that we have now adopted for the treatment of chronic osteomyelitis. The development and execution of the surgical technique employed has been the work of Dr. Louis G. Howard, Chief of the Orthopedic Service of the Massachusetts Memorial Hospitals.

For four to seven days before operation, penicillin is administered intramuscularly, every three hours, in doses of 15,000 to 25,000 units. Prior to operation roentgenograms are taken after the instillation of lipiodol into the sinus tracts. Stereoscopic views of the injected tracts are particularly helpful in estimating the location and extent of the tracts and in demonstrating their relation to areas of active infection within the bone. At operation the sinus tracts are excised, osteomyelitic cavities are exposed, and the sequestra and granulation tissue contained therein are removed. At the completion of the operation one or more soft-rubber catheters are inserted in the wound, which is closed in anatomic layers without tension and without drainage. Postoperatively intramuscular penicillin is continued until the wound is completely epithelialized. Local instillations of penicillin are made through the catheters every twelve hours for seven to ten days, at the end of which time the catheters are removed. The sutures are removed at the same time, or more commonly a few days later.

We have now treated thirty-five patients with a combination of penicillin and surgery. The period of follow-up observation, varying from two months to two and one half years, is much too short to permit any conclusions regarding the final results, but the immediate ones have been quite satisfactory. In all thirty-five patients the local lesion healed, and in thirty-one it has remained healed. In several cases it was not possible to remove all sequestra, and the four relapses that occurred were not unexpected. Two of these patients are now well as the result of a second operation performed in conjunction with further penicillin treatment.

In chronic osteomyelitis, as in the acute form of the disease, the changes in the roentgenograms are of no immediate value in assessing the response to therapy. In adults, in whom the infection in the bone has been well localized for a period of years, little or no change may be seen in the roentgenograms even a year or more after treatment.

In children and adolescents, however, definite improvement is frequently seen in the appearance of the bone but not until several weeks or months after the completion of treatment.

Even more significant than the response of the local lesion has been the effect of treatment on the patients' general condition. While some patients have shown little or no systemic reaction to their infection before treatment, many of them have presented the findings commonly encountered in a severe chronic infection; namely, poor nutrition, anemia, and weakness. Many of them have been unable to pursue useful activities because of their disease. Within the first month or two after treatment these patients have gained fifteen to twenty-five pounds in weight, their hemoglobin values and red-cell counts have returned to normal levels, and they have enjoyed a sense of well-being that they had not felt since the onset of their infection.

The most striking improvement that we have observed took place in one of the twenty patients treated with penicillin alone without surgery. This patient was a twenty-two-year-old man who had been ill for seven years with a chronic draining retroperitoneal abscess as well as a persistently active lesion in the femur. When he was first seen the liver and spleen were markedly enlarged and a Congo red test revealed 100 per cent retention of the dye in the tissues. Following two courses of penicillin separated by an interval of one year, the retroperitoneal sinus healed and drainage from the femur, which was not operated on, greatly decreased. At the completion of the last course of penicillin therapy, a Congo red test showed that only 57 per cent of the dye was retained in the tissues. In the next eight months the liver and spleen decreased in size so that they were no longer palpable. It is now a year and a half since his last treatment. The patient has gained seventy pounds and for the past year has been working full time without the loss of a day from work because of illness.

Before leaving the subject of chronic osteomyelitis, I should like to make it clear that we look on the patients in whom good immediate results have been obtained not as having the infection cured but as having it arrested. In most, if not all, cases viable bacteria are probably still present in the tissues, and given a suitable opportunity, the infection may well be reactivated. When relapses occur further treatment with penicillin and, if indicated, further surgical treatment should be carried out.

Bacterial Endocarditis

In discussing bacterial endocarditis, I shall confine myself primarily to a consideration of the acute form of the disease. The value of penicillin therapy in subacute bacterial endocarditis has been clearly demonstrated by the important contributions to this subject that have been made by several physicians in this city, notably the late Dr. Dawson[4] and Hunter,[4] Loewe,[5] McDermott,[6] and MacNeal[7] and their associates. The encouraging results that they have reported are familiar to all. Several problems remain to be solved, including those of the optimum dosage, the best methods of administration, and the value of adjuvant measures such as the use of anticoagulants, fever therapy, and the sulfonamides. One of the most interesting features of this disease is the absence of any clinical or laboratory criteria that will enable one to predict either before, during, or at the completion of treatment in which cases the disease will be permanently arrested by penicillin and in which it will be only temporarily suppressed. At the moment one can only follow the course of these patients. The finding of an organism that is susceptible to penicillin in a patient who is in good general condition does not necessarily ensure success, and the persistence of fever, embolic phenomena, splenomegaly, leukocytosis, and an elevated sedimentation for several weeks after the completion of therapy does not necessarily mean that treatment has failed. An extreme example of this statement is furnished by the following case.

Case 6. F. M., a 29-year-old man, had had the symptoms of subacute bacterial endocarditis for fourteen weeks before admission to the hospital. He had lost 60 pounds and had become bedridden. The day before treatment was started he had a cerebral embolus, and as a result he remained stuporous and partially aphasic throughout the entire time that he received penicillin. At present he has no memory of ever having received the drug. Prior to treatment two blood cultures positive for Streptococcus viridans were obtained.

At the completion of treatment, except for the fact that the blood culture was negative, the patient had shown practically no improvement. Although the blood culture remained sterile, he continued to have fever until 7½ weeks after treatment was completed. On the ninth day after stopping treatment, embolism of the right brachial artery occurred and new petechiae appeared almost daily for the next six weeks. Seventy-five days after treatment an enlarging pulsatile mass

over which a loud bruit could be heard, appeared in the right lower quadrant of the abdomen. It was thought to be a mycotic aneurysm of the right common iliac artery. It grew larger for ten days and then showed no further change in size.

It was not until six weeks after treatment was completed that we held any hope for this man's recovery. From that time on, however, his improvement was progressive. Six months after finishing treatment, he had regained his normal weight, there was no anemia, and the white-cell count and sedimentation rate were normal. For the last seven months he has been working full time as a draughtsman.

Acute bacterial endocarditis commonly involves previously undamaged valves and is usually caused by the ordinary pyogenic cocci; namely, the staphylococcus, the pneumococcus, and the hemolytic streptococcus, although cases due to other organisms are occasionally encountered.

It is well recognized that this disease manifests itself in two distinct forms—cases in which infection of the endocardium is primary and those in which it is secondary. In the primary form of the disease the patient presents the signs and symptoms of a constitutional infection without any evidence of localization. The blood culture is usually positive, but the diagnosis, particularly in the early stages of the disease, is difficult. Frequently it must be made by exclusion. The pathognomonic signs, such as the appearance of new or changing heart murmurs and the development of petechiae or other embolic phenomena, may be absent until late in the disease, and occasionally never develop. In such cases, the diagnosis may not be made during life, unless one is willing to conclude that the finding of one of the above organisms in the blood cultures over a period of several days in a patient who presents no signs of a localized infection is sufficient evidence for strongly suspecting the diagnosis.

Much more frequent is the secondary form of the disease, in which bacteria gain access to the blood stream from a frank focus of infection and only later become implanted on the endocardium. The diagnosis here may also be difficult, because again the pathognomonic signs are often absent and attention is usually fixed on the primary focus. It is not unusual in such cases for the diagnosis of bacterial endocarditis to be suspected only when progressive improvement in the primary lesion forces one to look elsewhere for the cause of the

patient's continuing symptoms and bacteremia.

It is doubtful whether before the introduction of penicillin any patient with the unmistakable signs of acute bacterial endocarditis, other than a few patients with infections caused by the gonococcus, ever recovered. During the last two years several patients in whom there could be no doubt as to the diagnosis of acute bacterial endocarditis have recovered under treatment with penicillin. It is not unlikely that others in whom the disease has not been diagnosed have also recovered. The results reported to date indicate that the recovery rate from acute bacterial endocarditis is approximately 45 per cent in cases caused by the hemolytic streptococcus, 35 per cent in cases caused by the pneumococcus, and 25 per cent in those due to the staphylococcus.

Little is yet known as to what constitutes an optimum schedule of treatment in this disease. This derives partly from the fact that in contrast to subacute bacterial endocarditis, in acute bacterial endocarditis the issue is usually settled rather quickly. The patient either recovers or succumbs to his infection within a few days, and there is little opportunity to experiment with dosage. Likewise, the fact that in many cases the diagnosis has not been established until after the patient has died, or occasionally until after he has recovered, makes it even more difficult to investigate the value of various treatment schedules. The next case illustrates the fulminating course that many of these patients follow.

Case 7. M. R., a 45-year-old woman, had been sick for only four days prior to her entry to the hospital. The sole complaints were fever and headache. Physical examination showed numerous pustular petechiae, but no abnormal cardiac signs could be elicited. The blood culture showed 4,000 colonies of Staphylococcus aureus per cubic centimeter. Following the administration of 200,000 units of penicillin daily the blood cultures became sterile, but the patient grew steadily worse, developed anuria, and died in shock after five days of treatment.

Autopsy revealed the presence on the mitral valve of several fresh bacterial vegetations from which Staphylococcus aureus could be cultured. There was no evidence of pre-existing valvular disease.

It seems clear that in most cases prolonged and intensive treatment is advisable, but it is quite striking that an occasional patient has recovered after relatively brief courses of therapy.

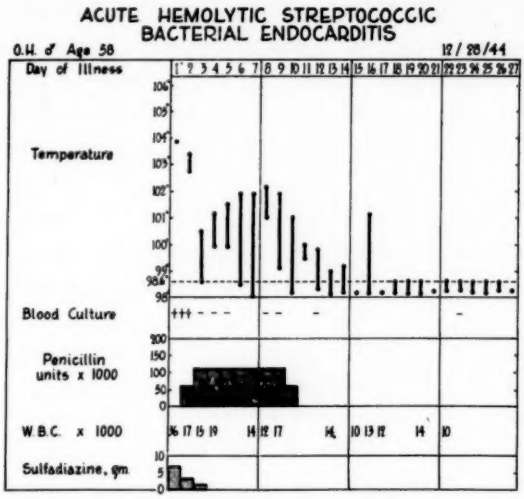

Fig. 6 (Case 8).—Chart of a patient with acute bacterial endocarditis caused by a B. hemolytic streptococcus. In this case an aortic diastolic murmur first appeared 22 days after the last positive blood was obtained and 13 days after treatment with penicillin was completed. This patient subsequently developed severe cardiac failure but no further signs of an active bacterial infection could be demonstrated.

In patients with acute bacterial endocarditis who have developed valvular defects, the appearance of severe cardiac failure after the infection has been controlled, has frequently constituted a serious obstacle to complete clinical recovery. Some of these patients have died within a few weeks or months from cardiac failure; others have remained seriously incapacitated.

One observation of considerable interest has been the fact that in several patients significant cardiac murmurs have not developed until one or more weeks after the infection has been eradicated and treatment has been completed.

Case 8. (Fig. 6). O. H., a 56-year-old man, developed an acute tonsillitis with high fever nine days before entry to the hospital. Sulfonamides were administered for five days, without improvement. On admission he was acutely ill. The only localizing signs of infection were a subsiding acute tonsillitis and minimal signs of bronchopneumonia in the left lower lobe. No cardiac abnormalities could be made out. Three blood cultures taken within the first twenty-four hours

were positive for beta hemolytic streptococci and intramuscular penicillin therapy at the rate of 15,000 units every 3 hours was begun and continued for eight days. At the end of this time the patient appeared to have recovered from his infection and the penicillin was discontinued. A low-grade fever persisted for a few more days and then disappeared.

The patient was allowed out of bed and was being prepared for discharge when on the twenty-third hospital day, thirteen days after the completion of treatment, a loud aortic diastolic murmur was heard for the first time. The patient left the hospital against advice three days later. Within three weeks he returned in severe cardiac failure, from which he was still incapacitated four months after the completion of treatment. Repeated blood cultures have been negative.

The appearance of aortic diastolic murmurs after the completion of treatment has been observed in other cases. Dr. Keefer has called attention to the fact that henceforth healed acute bacterial endocarditis, including both cases in which the disease has been recognized and those in which it has not been, will have to be considered as one of the causes of aortic regurgitation.

In conclusion, it can be said that the diseases discussed above are only selected examples of how the introduction of a new and potent chemotherapeutic agent may alter the course, prognosis, and management of disease. It is safe to predict that today we have only glimpsed the important changes that penicillin is going to effect in many of the common and uncommon infectious diseases encountered in medical practice.

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ON CERTAIN BIOLOGICAL FACTORS IN HUMAN DISEASE*

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As the vast discipline of medicine expands we can see ever more clearly how deep and complex are its bonds with the universe. For medicine deals with human disease and that in turn embraces man as well as his environment. The man is of special significance because he is the product of preceding eons during which, by slow and painful evolution, his fate has been determined. Those forebears who occupied lower branches on the tree of life struggled up from the ocean to gain a precarious hold upon the land. In the sea their bodily humors were at one with their environment, but as they came ashore protective mechanisms were devised to stabilize this inner medium which bathed their cells and to insulate them against an alien outer world. The adjustment to this change of atmosphere wrought hardships and provoked many varieties of biological design—some successful, others not. But one of life's main resources in its battle with a changing environment was its own infinite adaptability which has led to the complete individualization of each person. Through all these changes complexity mounted and after the establishment of an autonomic nervous and smooth muscle system which adequately mediated all the life-maintaining functions, the high if not always wise control by reason supervened.

In the past half century the transmission of all these accumulated characters has been shown to be effected by materials carried in the chromosomes of our germ cells. No man or woman can hope to escape the influences which flow from inherited chromosomal tissue, be they good or bad. Nor can the many protoplasmic products of these ever be expected to reach their appointed end unchanged. For the impressionable and reactive cell, within the limits of its nature, is inevitably altered to a greater or less degree by manifold forces from without. It

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is because of the foregoing reasons that individuals differ in appearance and that each reacts in a different personal fashion to any stimulus. The effort to comprehend the mechanism of these variations and how or why they become part cause of human disease is a major challenge to medical biologists.

The three sick people who provide the text for this essay are stationed at different points along the arch which spans the whole range of clinical medicine. The first was a Greek cook who had never known a sick day in the forty years of his life. For three months before his illness his business had been going badly, but he had not informed his wife of this fact because he did not want to alarm her. He admitted, however, that he was greatly troubled and said, "When you figure you can't make ends meet, that's sufficient." At the start of his illness he developed ten boils on his left thigh but sulfathiazole ointment sent him back to work in two weeks. One month later a large carbuncle appeared on the buttock accompanied by chills, aches and pains. Surgical drainage, supported with sulfathiazole by mouth, again returned him to work in two weeks. Eleven days after this chills and fever with more general aches and pains brought him to the hospital. Next day signs of spotty consolidation appeared, giving the impression of an interstitial pneumonitis, curiously enough without cough. The white count and the E.S.R. were elevated and the blood culture grew out hemolytic Staphylococcus aureus in all flasks.

Heavy dosage of sulfonamides and also penicillin controlled the infection and thirty-five days later he left the hospital cured. After his recovery he was fully aware of what the drugs had done for him and recognized that they had saved his life. "However," he said, "I was terrified all through and even in my delirium I was fighting to get back to fresh air and sunshine. I was ambitious to get well." His morale had been held high throughout.

The next person, who at six and one-half was as tall as a twelve year old, had been born with a perineal hypospadias. Five separate operations had failed to correct this condition. Then, as time passed, other inappropriate growth phenomena appeared. When he was seven, for example, his skeletal age equalled that of a twenty-five year old adult. In addition the child's musculature was precociously massive, hair excessive and voice low-pitched and strong. The penis was as large as that of a full-grown adult but no testicles could be found on physical

examination. Analysis of the 24 hour urine showed a 17 ketosteroid excretion of 29.6 mgm. One would normally expect 3 to 4 mgm. in a boy of his age. At operation, an almost complete set of female generative organs were found and removed. Dr. Earle Engle's report on these tissues follows:

"The ovaries with normal stromata resemble those of a prepubertal child. But in the mesovarium there was a mass 4 mm. in diameter which exhibited the structure of adrenal cortex. Throughout the removed tissue numerous rests of adrenal cortex were found. Apparently, there is no evidence of testicular tissue, although some remnants of the Wolffian (mesonephric) duct tubules are present."

In addition to the removal of the pelvic organs a partial corticectomy of a much hypertrophied adrenal gland was done.

The child possessed fair intellect and a certain mature poise but it was perturbed by its genital derangement and by the precocious development of form and exterior aspect, which belied its genetically predetermined sex. It was ill at ease and resented too close inspection.

Finally, the third person, an 18 year old Russian jewess, was completing her high school course, wherein she had achieved distinguished, although to her, unsatisfactory academic standing, when her menses diminished and her weight fell off. Her greatest weight had been 126 lbs. three years before she entered the hospital. At the time of entry she weighed but 71. On admission she gave a clear history of having been ridiculed by her schoolmates because of her fat body. She had no boy friends and spent all her spare time with her parents. There were no siblings. She was very short, approximately five feet one inch. Her face, broad in its frontal and bizygomatic areas, suddenly seemed to disappear at the chin. Her mandible was so small as to give the impression of the fetal jaw-skull relationship. Moreover, the teeth were diminutive, almost like deciduous ones, and each tooth stood separate from its neighbors. The hands were tiny and resembled those of a 6 or 7 year old child, and there was marked digital hyperextensibility. Her menses had begun at the age of 10 and they were regular until 3 or 4 years later when they gradually diminished and ceased altogether with the onset of weight loss. Constipation also supervened and this she could only combat by drinking 6-8 glasses of water. When her bladder was full she said she could move her bowels. She therefore displayed a tendency to polydipsia and polyuria. Recently an increased growth of hair on

extremities and face appeared. The basal metabolism was–36. There was also a delay in water output. Following the ingestion of 1000 cc. she required twice as long to excrete the excess as would the average person. This slow type of excretion is found in patients with anterior lobe pituitary deficiency such as chromophobe adenomata or true Simmonds' disease.

A detailed description of her clinical course would be superfluous here. It is typical, however, and fulfilled all the requirements of anorexia nervosa as laid down by R. F. Escamilla and H. Lisser[1] and by J. H. Sheldon.[2] Our present purpose, however, is not to discuss the differential diagnosis in the case but rather to point out that in the morphology and physiology there appear definite indications of genetic as well as growth and development faults. These faults are clearly in the system controlled by the pituitary-adreno-gonad assemblage.

Discussion

Every ailing person presents a unique clinical challenge, but these three have been selected to illustrate the biological common denominator which they share.

The first case presents an example of direct collision between an adverse element in the bacterial segment of the man's environment and his own personal immunity. It is of course well known that there are great variations in racial and individual powers of resistance to infection and practitioners have long recognized familial susceptibilities to given types of infectious agents. Observations of this kind point to the probability that genetic factors play an important part in such maladies. This concept is further supported by Webster's[3] demonstration of the inheritance of mouse brain susceptibility to encephalitic virus. It is also accepted that prolonged or transient adverse factors may reduce the threshold of resistance. Such commonly known predisposing factors as wet feet and over-fatigue from physical or emotional over-strain may act indirectly upon the immunity panel of man. But I have been unable to find impeccable evidence that symbolic traumata act directly upon this phase.

Our Greek cook could recall no chemical or physical resistance-lowering stimuli which preceded the boils. How much the man's anxiety over the threat to his business contributed to the specific lowering of his immunity mechanism cannot be determined by any definite method.

The suggestion that it did so must remain purely conjectural, but a denial of that possibility is equally without foundation. The major therapeutic plan was to support the man's failing immunity by general measures and to counterattack the staphylococcus with appropriate drugs. The cure in this instance was effected by the use of extraneous chemical agents—sulfonamides and penicillin. These substances grappled directly with an equally alien invader. The battleground, however, was laid within the patient's failing body, although the combatants, namely staphylococcus and drug, were both quite foreign to that structure. The implications in the account of his delirium, however, point obviously to the importance of any therapy which might lift his spirit and fortify his "ambition to get well."

The variety of troubles which the intersex patient has faced and will continue to meet throughout his life can be placed squarely at the door of congenital faults in growth and development. But to the wise physician will fall the task of guiding this biological anomaly toward a plan for the best possible adjustment to life. As is well known, in congenital errors both genetic and intrauterine factors often share the blame. Nowhere, however, is the situation more complicated, and still to a large degree obscure, than in the sphere of sex establishment. Most biologists agree that sex determination is not an absolute phenomenon by any means; but they accept the fact that the xx and xy chromosome combinations are potent factors in the process. These are the primal determinants of sex. Willier[4] has shown, for example, that in the 96 hour chick embryo the gonad rudiment (including the Wolffian body) can be transplanted into the chorio-allantoic membrane of a host embryo of either sex without altering the graft's capacity for self-determination. In other words, the indifferent gonad rudiment appears already to be organized as to its sex.

Contemporary students of endocrinology place great emphasis upon hormone control of sex. In the present case the evidence provided by the excessive 17 K.S. excretion and the hypertrophied adrenal cortex correlates positively with the clinical exaggeration of masculine characters and this notwithstanding the presence of female organs in the pelvis. But the truly remarkable thing about such a paradoxical situation is that the health and life of the individual is not necessarily threatened, only that of posterity. It would seem that so far as the first law of nature, self-preservation, is concerned the male or female character of the gonad

is unimportant. Indeed eunuchs and eunuchoids may live in good health to old age. Furthermore, as Lillie remarks, sex is "not an irreversible predestination but a quantitative over-balance in the direction of one sex or the other." The original sexuality is clearly determined by some interplay between sex chromosomes as well as by cytoplasmic contributions. In each new organism, therefore, the sex is established at the moment of fertilization, long before the appearance of Müller's ducts or Wolffian bodies. Following impregnation there exists a variable period of time during which the gonad type is not manifest. At the end of this time, when the nature of the gonad is declared, the endocrine glands begin to function and exert powerful influences upon the physiology of the maturing individual. As A.E. Severinghaus[5] writes:

". . . it has been established beyond question that 'genic balance' (xx, xy) in the chromosomes of germ cells sets up either a male or female pattern, which under normal circumstances will develop into an individual of specific sexuality. In man the pattern is so delicately balanced that additional factors may stay or change the original course of development. Thus, while sex pattern is determined by genic balance in the chromosomes, the successful achievement of that pattern is dependent upon proper superimposed influence of hormones."

However, the hormones cannot alone be responsible for their superimposed influence upon the embryo of which they are themselves a part. The same chromosomal stamp which the endocrine cells bear affects all the cells of every tissue in the body. The latter can only respond to the circulating hormones in a manner equally specific as that which marks the secreting cells themselves. Thus, in the case of a genic male pattern, for example, the production of androgens (17 K.S.) is presumed to be higher than the estrogens, and the body cells to be appropriatively reactive. In females the reverse is expected. In the present instance the genic plan had evidently been for a female, but unknown faults in development led to great over-production of androgen by the hypertrophied and scattered adrenal cortex. The original design was thereby greatly disturbed.

Possibly the foregoing mechanism determines the important phenomenon known as the androgynous mosaic; maleness within the female and femaleness within the male. The gonads themselves are chiefly concerned with posterity through the production of egg and sperm. The effects of their hormones are to large extent determined by

the nature of the extragenital tissue cells which they bathe.

So far as the individual's sense of personal security, or ego identity, is involved, it is essential that the androgyny, or extragenital phase of sex should be clearly appropriate to the genic or primary sex plan. Any diminution in a female's sense of preponderant femininity or any awareness of elevated masculinity may arouse unexplained doubts from which flow multiple apprehensions. Precisely the reverse of this situation occurs in the genically preordained male. In his case even minimal emphasis upon the feminine character may be bitterly resented and confront him with a fear-provoking threat. It is not easy for the average male to accept his genic endowment of feminine characters with equanimity. For, notwithstanding the fact that they may be of value to him in situations where the faculties of intuition, sensitiveness and understanding are required, he is more apt to resort to one of the two other available courses of action, flight or fight. Either the adolescent, gynic-stamped male will retreat to the maternal protectorate, which is often masked as chronic invalidism, or he is driven violently by a compensatory andric urge which may lead to heroic exploits or to alcohol, venery and final frustration. The energy which mobilizes such conduct is gathered from every cell in his body.

Although all these extragenital manifestations of sex exist, the popular term "sex problem" is commonly used to refer to tragedies which color the intimate relationships of men and women. Indeed, psychiatry and psychoanalysis have not especially emphasized the significance of sex biology until Zilboorg's[6] recent fine review of the subject. It is notable that from the Biblical admonition "Go, and sin no more" down to the Freudian formulations the biological foundations of human sex conduct have been undervalued. And from the Delphic oracle, through the history of Catholicism, to the present era of psychotherapy, people have always been more strongly moved by the mystical dissolution of ailments than by the demonstrable mechanisms of their own natures. Moreover, the psychoanalytic thesis of retardation and arrests has emphasized the concepts of sin and guilt which always grow up like weeds about a shattered totem or taboo. Such crimes subject the miscreant to fear of punishment which is expressed in mental confusion and suffering or in the so-called conversion phenomena observed in the signs and symptoms of bodily disease. But, from the medical biologist's point of view, problems in sex are only those resulting from the twisted inter-

play of heredity and environment on body protoplasm. Sex problems in the popular sense, on the other hand, actually turn out to be fear problems. And so, fear, that master stimulus to the physiology of self-preservation, promptly mobilizes adrenalin which variously influences each and every tissue cell.

In view of the powerful genetic and endocrine forces, which by their faulty expressions establish the biological basis for threats to life and ego, it is difficult to understand how post-natal emotional factors alone can have so great a bearing upon sex-motivated conduct as some have attributed to them. On this point one is forced to question the arbitrary position taken by Freud[7] in his third preface to "Three Contributions to The Theory of Sex." He writes:

"Besides its thorough going dependence upon psychoanalytic investigation I must emphasize as a character of this work of mine its intentional independence of biological investigation. I have carefully avoided the inclusion of the results of scientific investigation in general sex biology or of particular species of animals in this study of human sexual functions which is made possible by the technique of psychoanalysis."

Freud himself, of course, like any other independent investigator, is not to be criticized because he chose to repudiate the stern discipline of scientific method or that he espoused a speculative and literary approach to the vital responses of living forms. He possessed the same kind of personal conviction which has led other great men to change their political or religious beliefs and that is to be respected. But in the face of well-established and growing knowledge of biological fact can we physicians who purport to be interested in the ailing man as a total organism, wisely make such a sweeping exclusion of those physical and physiological elements which compose the living presence of the patient? How can the neurotic conduct which is said to arise from infantile sex thoughts and phantasies, as portrayed in dreams and odd behavior, be thoughtfully comprehended unless the genetic, anatomic and physiological substrates of sexuality be properly assessed?

If, for example, it is assumed that emotion arising de novo from the penumbra penetrates the entire organism and starts hormone secretion, the protoplasmic reaction thereby provoked in the body cells must still depend to large extent upon the genetic nature and conditioned habits of those very protoplasms. Moreover, as has been recognized for many

years and much emphasized by Adler[8] and other psychoanalysts, the threat to security, based on an inner sense of corporal incompleteness or inadequacy, is the parent of fear. Consequently a clear understanding of the patient's biological faults may help the physician to comprehend that fear and allay it through an educational form of therapy. But in addition, certain symptoms which arise from lesser maladjustments in the androgyny can often be helped by appropriate use of hormones.

The very name anorexia nervosa at once implies that the major cause of the young Russian girl's sickness is "purely" psychological. Moreover, the psychiatrist's note in her chart states that "from the psychiatric point of view this is a very typical case of anorexia nervosa." But, because of the obvious faults in the patient's physical growth and development, there is much to be said for a physical and physiological origin of the malady. Indeed, those stigmata are so emphatic and so often seen in other similarly afflicted persons that one is justified in saying that this individual is a typical representative of those persons who may express their inadequacy in this strange disease picture. Though her 17 K.S. excretion of 10.3 mgm. for 24 hours is within normal limits there are morphological indications of more than average emphasis upon the andric component. These are to be seen in the heavy bones and big joints, the wide shoulders, the contours of the thighs and legs and the distribution of muscle tissue which became visible as fat disappeared. More noticeable, perhaps, and more consciously appreciated by the patient herself, was the loss of menstrual function and the increase in hair which grew in andric patterns. As was mentioned in the preceding discussion, the concept of inappropriate or incomplete sex differentiation constituted a basic threat to ego security. The starting point of the girl's difficulty may well have been the deep inner confusion produced by the congenitally distorted sexuality. The overemphasis upon her andric component was only sufficient to stimulate but not to satisfy what psychoanalysis has termed the "masculine protest." It is interesting in this connection that perhaps the first symptom was the disappearance of menstruation. From then the neurosis developed increasingly. Her ostensible reason for reducing her diet was the fear of being ridiculed as obese. This rationalization was re-enforced by her lack of masculine admirers. But the genetic stamp and the subsequent growth and development asymmetries had prepared the way. All of the reported characteristics which are in the zone of the pituitary-

adreno-gonad control are obviously the product of her chromosomes in collaboration with the intrauterine and post-natal environment. In this patient they show a strong andric trend. When these chromosomal foundations are very skew, one can expect vital functions to deviate from normal to an increasing degree as the pressure of life increases with age.

The stories of these three sick people hold a deep significance for us. They illustrate that beneath each clinical syndrome there is a complex common denominator composed of human protoplasms and their sharply individualized expressions. Underneath them all lie the protoplasmic factors which were originally brought up from the sea. Some of these ancient characters, shared by every animal species which has existed, are now demonstrable. Recently Schmitt, Hall and Jakus[9] have shown by means of the electron microscope that collagen fibrils of identical structure are found in a variety of living forms and of some living fossils, such, for example, in reverse order of remoteness, as mammals, amphibians and mollusks. New and divergent mechanisms which developed in response to new demands of environment have resulted in the differentiation of the species, and then, within the species, of individuals. The latter likewise display great diversity not only between total personalities but even in the cell type pattern which each man's leukocytes develop in vital cultures of the buffy coat of his blood.[10] These recent findings reflect Landsteiner's[11] vision and later demonstration that different individualities could be recognized in the cellular and chemical nature of the blood itself. And this fact Landsteiner believed was a parallel phenomenon to the specificity of tissue transplants which has long been known to surgeons and recently so well demonstrated by Leo Loeb.[12]

The chromosomes of our germ cells contain all these ancient and recent characters which dominate the descendent individuals and their separate parts. Then, through some accident of breeding or nurture, the established balances are disturbed and the resulting imperfect creatures are cast upon the world. In their effort at adjustment the vital reactions of these inadequate individuals become the signs and symptoms of disease which drive them to us for relief. Being physicians we are obliged to deal with them as best we may, according to the established laws of nature.

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A CRITIQUE OF PSYCHOTHERAPY IN ARTERIAL HYPERTENSION*

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IN considering the complicated subject of arterial hypertension it is appropriate at this time to review the experiences with psychotherapy. Both in this approach and in others there is admittedly a great deal that we do not yet know. Professor George Santayana used to talk about defining the limits of our ignorance. What are these limits?

We do not know, for example, whether the process is a reversible one, whether the impulses which give rise to arteriolar constriction are humoral or neural in origin, or both. In spite of the brilliant researches of Goldblatt[1] and others, we do not know what part the kidneys and the renal circulation play in bringing it about. Indeed, it would be hard for us to define this disease further than to say that it represents a morbid state in which elevation of the systolic and diastolic blood pressures—either fluctuating or constant—occur in association with arteriolar vasoconstriction. We do not know why the life expectancy of some is unaffected while others succumb quickly to the malignant form.

Once we thought that hypertension was associated with a certain bodily habitus—that it was more prone to exist among the short and the squat and the red-faced. Those of you who have occasion to see patients suffering from this disturbance have found them to be lean and spare, tall and pale-faced as well. According to Page,[2] "an accurate correlation of body build, height and surface area with arterial pressure cannot be established". Again citing Page as my authority, and contrary to generally accepted beliefs, there is no sufficiently documented testimony to support the view that heredity plays a vital part in the genesis of hypertension. He cautions against ascribing too great importance to heredity and suggests that this aspect of the problem needs reinvestigation on a more comprehensive basis.

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This then is part of the staked-out claim of our ignorance. To outline it is not to underestimate the importance of recent researches and their contribution to our understanding of the physiological mechanisms of this disorder.

That it has still another aspect is now rather generally accepted. In this terrain our ignorance is even wider and more varied. It would be a challenge, indeed, to plumb its depths and to chart its perimeter. I am speaking now, of course, of the psychological aspects of arterial hypertension which some have attempted to explore: Alexander,[3] Menninger,[4] Moschowitz,[5] Rennie,[6] Saul[7] and Weiss[8] among others. In collaboration with Nathan Ackerman,[9] I have myself put in four years at hard labor breaking ground. I cannot say that we struck gold, but I hope at least that we uncovered some facts. These are to be published in a much over-due monograph of which the page proof has finally come through. The work was supported by a grant from the Josiah Macy, Jr. Foundation and was done in coöperation with Drs. Cohn, Schroeder and Steele of the Hospital of the Rockefeller Institute. The investigation was based on the clinical and psychiatric study of 24 patients suffering from arterial hypertension.

I should like to say here in parenthesis that the description of the personalities of these patients which I shall presently offer and which derives from our own work and, in part, from that of others does not, in all probability, apply uniquely or exclusively to the hypertensive state, though none of our patients differed widely from it. I have, myself, yet to be convinced that characterological studies made by those interested in psychosomatic medicine have any specific etiological significance. Not beauty alone but artefacts as well may dwell in the eye of the beholder.

The facts that appear from our own studies and from others' are these: Sufferers from arterial hypertension exhibit a disorder of personality which has been conveniently described by the term "neurotic." This disorder manifests itself in their inter-personal relationships, in their sexual adjustments and often in their occupational achievements. They are characteristically tense individuals given to states of anxiety and depression. Much of their emotional tension can be ascribed to inhibited, but not deeply repressed, aggressive impulses. It is often possible to trace the history of this neurotic development of character to early childhood when the common feature is an extreme degree of

insecurity, with a greatly unsatisfied dependent relationship to a threatening parent. Given this bad start the patient then falters through life—unable to relax, unable to enter into secure and satisfying relationships, always on the defensive, ready to fight but afraid to fight.

With this precarious adjustment the apple-cart of the patient's emotions is easily upset. The death of a parent, or partner, a motor accident, the illness of a child, business reverses—almost any event which jeopardizes his security—which is felt either directly or by implication as a threat to his life—increases to an intolerable degree the quantum of his anxiety and of his reactive depression. In our series of cases it was observed that the clinical discovery of elevated blood pressure frequently coincided with such a traumatic experience.

I do not wish to be understood as stating that this disturbance of character or its ultimate outcome is the cause of hypertension. It is, on the contrary, my suspicion that the psychological disorder and the physiological disorder each represents a different aspect of a more basic disturbance, the nature and cause of which is unknown—though its existence is often foreshadowed early in life.

What therapeutic implications are to be drawn from these observed facts and from this theoretical interpretation of them? The first is that psychotherapy cannot be directed at blood vessels. It can be directed at the emotions. Its aim is to treat the person, not the vaso-constrictor mechanism. This must be kept clearly in mind. What we can accomplish will depend—as in any other therapeutic procedure—not only upon our skill, but also upon the material with which we are forced to deal. It is not a plastic, easily workable one. These patients have usually extraordinarily rigid personalities. Their aggressions are fixed, they are not fluid or readily mobilizable. If they were, they themselves would have spontaneously found a more satisfactory and less destructive expression for them. Much of their anxiety is absorbed in their symptoms. It is not easily dislodged and when it is it may sweep over them and produce a state bordering on panic. The underlying depression is constantly being fed by the conviction that they are sufferers from a fell malady, that fate has dealt them a body blow. Each symptom winds up the main spring of their tension, increases their anxiety and undoubtedly reflects itself in their vascular apparatus. Deep psychotherapy in this illness is, therefore, no task for the bungler or the amateur. It is as dangerous, as delicate and as difficult as surgery.

Like the surgeon the psychotherapist must know something of the topographical anatomy of his patient. His aims are to restore a more normal functioning of the emotions. Persuasion and reassurance, though important tools, are seldom sufficient. They will not remove tough bands of connective tissue and they will seldom remove the strictures and inhibitions against which these patients live their unfulfilled lives.

Again like surgery, the choice of procedure will depend not upon pre-conceived doctrinaire generalizations but upon careful clinical observation. It is as absurd to say that every patient suffering from hypertension should undergo psychoanalysis as it is to say that every case of neoplastic disease should be operated upon. The decision is based first of all on the patient's ability to stand operation, secondly upon the nature of the lesion and its accessibility, and thirdly upon the prospects for a successful result. Surgeons no longer operate because there is nothing else to do, but rather for specific reasons empirically derived. In the domain of psychiatry and psychoanalysis the same critical standards are now happily being invoked.

The surgeons have, to be sure, a great advantage over us; not only is their handiwork more precise, but their results are referable to a statistic which it would be folly to assert that we possess. We have none.

Lacking a statistic we can at best proceed according to certain rational principles. I have stated what they are. The problem is that of treating a severe character neurosis in which anxiety, depression and suppressed aggression are the cardinal psychopathological features. The method of choice will vary from cheerful neglect (based on that much vaunted common sense which we are all supposed to possess in such good measure) to deep psychological exploration. The latter you will grant is a matter for the expert. What is to be hoped from it we cannot say. There is as yet no evidence that psychoanalysis or any other psychotherapeutic procedure can reverse the physiological process or change the destiny of this disease–be it benign or malignant. The problem is an open one. It needs further investigation. The ground has now been cleared for such an undertaking. It is probable that we can do more by way of prevention than cure.

There is evidence that a correlation exists between levels of pressure and emotional disturbance and that suitable psychotherapy can ameliorate some symptoms: such as headache, fatigue, palpitation, dizziness, shortness of breath and the fear which these engender.

We have observed this ourselves and so have others. Weiss[10] has stated for example: "For some time now I have felt and taught that essential hypertension cannot be eradicated by any psychotherapeutic process but that almost every patient can be benefitted by psychotherapy". In a review[8] of the records of 200 consecutive patients with symptoms of hypertension he selected 144 which "seemed to correspond to the clinical picture of so-called essential hypertension" (note the cautious conservatism of his words). Ninety-three of these lent themselves to satisfactory psychosomatic investigation and in only seven did he conclude that psychic factors bore no relationship either to the onset of hypertension or to the production of symptoms. Case I. of his series shows a quite remarkable coincidence between periods of elevated blood pressure and vaso-spastic retinitis with anxiety producing episodes and with what Weiss calls periods of "throttled aggression."

In Alexander's[3] carefully studied psychoanalytic material he presents blood pressure readings of 161/110 when his patient was emotionally disturbed as compared with 142/98 when calm. Saul[7] has made similar observations of fluctuations of blood pressure with mood and, more especially, with variations in the intensity of the so-called transference situation. It must be borne in mind that fluctuations may occur spontaneously without reference to known therapeutic effects.

The most striking, unique and dramatic case in the literature is a patient of Lewis B. Hill,[11] who recalled early in the course of psychoanalytic treatment a deeply suppressed childhood memory. This was brought up with intense effect. The patient exhibited an extraordinary degree of rage and guilt over a childhood experience in which his mother struck him with a pony whip. The recall and reliving of this traumatic episode was followed by a critical sustained and enduring fall of both systolic and diastolic pressures. Perhaps this single observation is a prototype of others to come. But, in honesty, it must be said that from a clinical and physiological point of view the case is insufficiently documented and the diagnosis remains open to question.

Leaving now out of consideration all efforts at deeper psychodynamic inquiry and turning to the every day handling of these patients, I believe that our new knowledge can be put to effective use. We are dealing with tender vessels. They need to be protected from emotional strain, especially from demands upon a self-reliance they do not possess. There is no good in telling them to "buck up" and "forget

it." They need the maximum of reassurance about the disease itself. They need very much to feel that some one person is watching over them and will take on his shoulders the burdens of their worries. They need to be encouraged to express their aggression, not by hurling dishes or epithets at their wives, but by directed work and play and by physical exercise, if this is compatible with their cardiac reserve. They need to be weaned away from an over-concern with the level of their blood pressure. The experienced doctor will vary his methods. With some he will be frank, with others he will be silent and to some he will have to dissemble. The manner in which this frightening fact is first presented to them is of the utmost significance. If the doctor shows his own alarm when the mercury column tops 220 it is likely to be communicated at once to his patients.

It is well to remember that almost all our therapy is in essence psychotherapy. Drugs and sedatives, rest and exercise, diet and baths all have psychotherapeutic implications; and this is just as true of surgery. The surgical amphitheatre has become the court of last resort in this illness. Perhaps in time we will learn on what findings nature bases her verdict—why some patients respond to sympathectomy with a reduction in blood pressure, a recession of retinitis and a merciful relief from headache, while others do not. I hope that it will not be thought too "tender-minded" of me if I suggest that the attitude which patients bring to the ordeal of operation may in some measure determine its effect upon them. For there are those who face it as they would doom and there are others who look upon it as a deliverance.

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TRICHINOSIS: A MAJOR HEALTH PROBLEM IN THE UNITED STATES. WHAT SHALL BE DONE ABOUT IT?[1,2]

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HISTORICAL

TRICHINOSIS is a disease which probably dates back to antiquity. It is believed to have been responsible for the Mosaic law which prohibited the Israelites from eating the flesh of the pig. The parasite, however, was not discovered until 1835. In that year, James Paget, then only 21, and a first-year medical student at St. Bartholomew's Hospital in London, encountered in the muscles of a human subject in the dissecting room, minute whitish spots, which when examined under the microscope were found to be cysts, each enclosing one or more little worms. The cysts were further studied by Richard Owen, who named the parasite *Trichina spiralis*. The present name, *Trichinella spiralis*, was given to the worm by Railliet in 1896. The trichina was first found in the meat of the hog in 1846 by Joseph Leidy, a Philadelphia physician and naturalist. Leidy noticed minute whitish specks in a slice of pork which he was eating. These specks struck him as being similar to trichina spots which he had seen in the muscles of a human subject at autopsy only several days previously. He examined the remainder of the meat microscopically and found it full of trichinae.

The ability of the worm to produce disease in man was first recognized in 1860 when Friedrich von Zenker, a pathologist in Dresden, Germany, discovered the life cycle of the parasite. In that year, a 20-year-old servant girl, diagnosed as having typhoid fever, was brought into a hospital and died about thirty-three days after the onset of her illness. Zenker examined muscular tissue taken from the arm of the patient at autopsy for degenerative changes characteristic of typhoid fever but instead was startled to find numerous trichinae which exhibited obvious signs of life. Zenker's further investigations with regard

[1] Read before The Society of Medical Jurisprudence of New York, May 14, 1945.
[2] From the Departments of Pathology, Wayne County General Hospital, Eloise, Michigan and Wayne University College of Medicine, Detroit.

to this case sound like a modern detective story. He found larval worms in all the skeletal muscles and mature adult worms in the intestines of the patient. Zenker visited the household in which the servant girl worked and found trichina larvae in the ham and sausage that was prepared from a pig that had been slaughtered 4 days prior to the onset of the girl's illness. In addition, all the members of the household, who had eaten of the meat of this pig, had fallen ill. He concluded that the entire cycle of development of this parasite could take place in one host and that the trichina larvae were probably disseminated through the body by way of the lymphatics and blood stream. These conclusions are now known to be correct.

Soon after Zenker's discovery there occurred in Germany two notable epidemics. In the first epidemic which occurred in 1863 in Hettstädt, a town with a population of 4,000, 158 persons fell ill, of whom twenty-seven died, a mortality rate of 17 per cent. In the second epidemic which occurred two years later in Hedersleben, a town with a population of 2100, 337 persons fell ill with trichinosis, of whom 101 died, a mortality rate of 30 per cent. These two epidemics brought forcibly to the attention of the medical profession of Germany the great danger of eating uncooked pork. As a consequence there was soon instituted in many parts of Germany a compulsory system of microscopic inspection of pork, and the meat of every animal found to be trichinous was destroyed. Similar systems of inspection of pork have been in force in other countries of the world, including Sweden, France, Argentina, and Chile. Between the years 1891 and 1906 the United States Department of Agriculture was authorized by act of Congress to inspect all pork which was intended for export since American pork had largely been excluded from European markets on account of its frequent infection with trichinae. The Act of Congress authorizing microscopic examination of pork did not however achieve its purpose and such inspection in the United States therefore was discontinued in 1906. The label, "U.S. Inspected and Passed" on pork has no reference whatever to the presence or absence of trichinae, since non-processed pork bearing this label may contain living trichinae. The Federal Government does not examine pork microscopically.

Method of Infection

Man acquires the infection almost exclusively from the ingestion of

pork containing viable trichinae. The pig acquires the infection primarily from the consumption of bits of raw trichinous pork in uncooked garbage. The meat fibers and the walls of the trichina cysts are digested in the stomach of the host, liberating the living trichina larvae which develop within a few days into sexually mature adult forms in the small intestine. Beginning at the end of the first week of infection and continuing for a number of weeks thereafter, the gravid females, imbedded in the mucosa of the bowel, deposit their living larvae into the mucosa, whence they enter the lymphatics and then the blood stream, traverse the capillaries of the lungs to reach the left side of the heart and are then thrown into the general systemic circulation whence they finally enter the striated muscle fibers. At the time of birth, the larvae measure approximately 100 microns in length and 6 microns in diameter, the diameter therefore being somewhat less than that of a red blood cell.

Symptoms

Withing the skeletal muscles the larvae enlarge and set up an inflammation which is responsible for many of the symptoms of the disease. At 17 days after infection, the larva begins to coil and at about thirty-five days after infection, it reaches its maximum growth and then begins to encyst within the muscle fiber which has undergone degeneration. The degeneration of the muscle is attended by considerable inflammation and edema and in heavy infections the inflammation and edema may be so marked as to give rise to violent symptoms. In such severe infections, trichinosis may truly be a "terrible" disease. Indeed, movement may be so painful that the patient may lie in one position constantly for days, afraid even to move his eyes or his tongue, to speak, or even to swallow. The heart is regularly invaded by the parasite and an inflammation is set up within the myocardium. In moderately severe or in heavy infections, the myocarditis may be dangerous since it may cause sudden death or may lead to heart failure. After some weeks, depending upon the severity of the disease, the inflammation in the heart, as in other striated muscles, subsides. Within the skeletal muscles, the parasite if not destroyed, becomes well encapsulated and may remain viable for many years. Within the heart, however, the parasite is regularly destroyed even though it has set up a severe inflammation. Encystment of *Trichinella spiralis* within the myocardium never occurs. An-

other danger of trichinosis is that which results from capillary damage and petechial hemorrhages within the brain. Encephalitis and meningitis sometimes are found in acute fatal cases. The *incubation period* varies from two to twenty-eight days with an average of ten days. The disease has been divided into the following stages: (a) intestinal, (b) invasive, and (c) convalescent. Most of the symptoms are due to the effects of invasion of the newly-born larval parasites. Particular mention may be made of supraorbital edema and fever, of the diagnostic sign of eosinophilia, and of electrocardiographic evidence of myocarditis.

Diagnosis

Eosinophilia is the most important single diagnostic sign in trichinosis. It begins to appear as early as the tenth day, and reaches its peak during the third week of infection. There are several other laboratory tests of diagnostic value. An immediate type of allergic response may be obtained following the intradermal injection of a trichina antigen in a dilution of 1:7000 or 1:10,000. This "immediate intradermal reaction" may be elicited on and after the 17th day following infection. Specific blood precipitins and complement-fixing antibodies may be found on and after the 28th day of infection. The demonstration of larvae within the blood, cerebrospinal fluid, or the skeletal muscle of the host is of prime importance in establishing the diagnosis. Trichinae may likewise be demonstrated in portions of uneaten suspected meat. In the examination of muscle from the patient during life, the following methods may be used to detect trichina larvae: 1) microscopic examination of fresh muscle within a compressor or "trichinoscope", 2) maceration of muscle to detect young larvae which have not yet attained their full growth, 3) digestion of muscle tissue of the patient at 37° C. for eight to 12 hours, using a digesting fluid which consists of 1 per cent hydrochloric acid and 1 per cent pepsin, and 4) biopsy. Serial microscopic sections should be made if necessary of the tissue taken for biopsy. The diagnosis of trichinosis is often not easy and is frequently missed since the symptoms may simulate those of numerous other diseases. When the correct diagnosis is suspected, appropriate methods of examination will usually enable one to demonstrate the existence of the parasite.

Treatment and Prevention

Treatment is largely symptomatic. Bed-rest should be prescribed

until all danger of heart failure or of complications has passed. There is no specific remedy except that of prevention. At the present time, prevention is largely up to the ultimate purchaser or consumer of pork and consists principally in thorough cooking or sufficient heating of the pork and pork products. The Federal government recommends that pork should be boiled at least thirty minutes for each kilogram of weight (2.2 lb.). Another approximate guide for thick cuts of ham or pork is to cook them one-half hour per pound. All portions of cooked pork should be white. Trichinae may also be killed within pork by methods of freezing. In order to destroy by freezing living trichinae within cuts of meat not exceeding six inches in thickness, governmental regulations require that a temperature of not less than 5° F. be maintained for at least 20 days. Incidentally, this temperature is within the range of deep-freeze cabinets, such as are used in the home.

Incidence of Trichinosis in United States

In 1932, the meat of 14 million hogs was subjected to microscopic examination in Prussia and trichinae were found in only 0.001 per cent of the animals or in 9 hogs per million. In 1933, the meat of 14 million hogs was similarly examined and only 0.0008 per cent or eight animals per million were found trichinous. During the years 1898 to 1906, the meat of 8 million hogs was microscopically examined in the United States and 1.41 per cent, or over 14,000 hogs per million, were found trichinous. The average incidence of trichinosis among hogs in the United States at present is as follows: 0.4 per cent of hogs which are fed cooked garbage, 0.8 per cent of hogs fed grain, 6.4 per cent of pigs fed uncooked garbage and 15 per cent of animals fed slaughter-house offal. A conservative estimate of the average incidence of trichinosis among hogs in the United States at the present time is 1.5 per cent. Each year about 90 million hogs are slaughtered in this country. If 1.5 per cent of these are trichinous, and if each hog furnishes meat for about 100 meals, there will be consumed within the United States each year 135 million meals of pork containing trichinae. Fortunately, of course, in most instances the trichinae will have been killed. Too often, however, live trichinae will be ingested and it is no wonder, therefore, that in recent surveys of autopsies in the United States, an average of 16 per cent of the population should have been found to harbor trichinae. This figure is low, for when more thorough investigations are made,

the incidence at autopsy has been found to be as high as 36 per cent. It would be a conservative estimate to state that approximately 25 per cent of the general population of this country develop trichinous infection during their life-time. In other words approximately one person in every four becomes infected with this parasite. Fortunately the infection is subclinical in the majority of cases. It is estimated that at least 5 per cent of those who become infected show signs of illness but that only about 1 per cent of all who are infected become sufficiently ill to confine them to bed with clinical trichinosis. The mortality rate from clinical trichinosis in the United States is 5 to 6 per cent. It has been said that "trichinosis is one of the major health problems in the United States" and that "the United States has the greatest problem of trichinosis of any country in the world." At the present time, the public is not sufficiently protected against the dangers of this disease.

Medico-legal Aspects

From the medico-legal standpoint, the manufacturer or packer warrants to the public generally that the food which he produces is fit for human consumption. If the consumer becomes ill with trichinosis, the manufacturer or packer of the trichinous pork may be held liable because of his negligence in the preparation of the food or because of breach of the implied warranty of wholesomeness and fitness of food which is sold for human consumption. The majority of claims have been based upon the breach of implied warranty and in most instances judgment has been rendered for the plaintiff.

Control Measures

Since pork is a desirable food, being rich in protein and fat and very rich in vitamin B_1 (thiamine chloride), is usually easily digested, is savory and nutritious, is it not amazing that the public should have to consume it so often at the risk of health and life? The danger of trichinosis appears to be particularly great in the case of sausage made with pork which is raw or insufficiently cooked or under-processed. The situation today in regard to the control of trichinosis may be likened to that which prevailed in the dairy industry of this country thirty or more years ago, prior to the general adoption of pasteurization of milk. Certainly no one will now argue the value of effective pasteurization to the public as well as to the dairy industry. For similar reasons, methods

which are known to be effective in the destruction of living trichinae in pork and which do not produce injury to the quality of meat should be adopted throughout the United States at the earliest possible moment. The costs of instituting measures which will safeguard the health of the public must of course be borne eventually by the consumer but, as in the case of pasteurized milk, the consumer will be glad to pay this small extra cost in order to have the added measure of protection. Incidentally, such protection must inevitably lead to a greater salability of pork products and a greater willingness on the part of the public to consume pork. The adoption of such protective measures by the packing industry will be found to constitute good business practice.

Granted that some method should be adopted for the protection of the health of the public, let us consider what methods of controlling trichinosis are available and practical. In general there are three available methods of control, as follows: 1) microscopic inspection of meat from every slaughtered hog, 2) cooking of all garbage that is to be fed hogs, and 3) processing of all pork to render it free from viable trichinae.

1. *Microscopic inspection of pork.* Microscopic inspection of pork requires that one or more specimens of muscle from every slaughtered hog shall be examined under the microscope for the presence of parasites. The arguments that this method is too expensive and too time-consuming for present-day high-speed American needs are ridiculous. No expense is too great as far as the health of the public is concerned. Furthermore, there are rapid methods of examination, such as the "phototrichinoscope." Additional time-saving methods would no doubt be devised if necessary. Other countries have found microscopic inspection practical and the method has been in vogue in Germany, France, Sweden, Argentina and Chile, in most instances for many years. The Act of Congress which, beginning in 1891, authorized the inspection of all pork which was intended for export, was repealed in 1906, principally because the German government did not accept the certification of the U. S. Department of Agriculture that the pork bearing its label was free from trichinae. The chief valid objections to the inspection of pork are 1) there is a large human error in the microscopic inspection, 2) trichinae may not be found in the particular specimen of muscle examined, and yet be abundantly present in other muscles, and 3) the public may acquire a false sense of security in

eating pork raw, since it has passed microscopic inspection. Thornbury, in 1897, failed to find trichinae in the diaphragm of approximately 24 per cent of 1043 trichinous hogs in which parasites were found in one or more of three muscles examined. It is principally the diaphragm from which specimens are generally taken in the microscopic inspection of pork.

2. *Feeding of cooked garbage to hogs.* The feeding of cooked garbage to hogs would be an effective method of control if it could be universally enforced. Such enforcement appears to be possible in the case of large growers of swine, but it would be practically impossible to control small producers of pork and farmers who raise small numbers of swine. This method of control is considered to be the least practical of the methods which have been advocated.

3. *Processing of pork.* Under the term "processing" are included methods of refrigeration, cooking, smoking, salting, and any other means which may be employed if carried out according to regulations set forth by the U. S. Bureau of Animal Industry for methods which are effective in destroying viable trichinae within pork and pork products. At the present time the only pork products which are reliably free from living trichinae are those which are manufactured in plants operating under governmental supervision, the products being processed according to Federal specifications so that they may be eaten without further cooking. If the Federal government would require that *all* pork and pork products which are shipped in interstate commerce shall be so processed as to render the meat free from viable trichinae; and if local and state health authorities would adopt similar regulations for pork which is sold locally or within the state, and if in addition, the Federal government and/or the local and state health authorities would require that all pork offered for sale bear the label "This product conforms to Federal and/or local or State regulations for processing of pork"; we would then have an effective method of control of trichinosis. Such a method would obviate the dangers present in microscopic inspection and the weaknesses which are inherent in laws that require that only garbage which is cooked may be fed to hogs. The responsibility for the proper manufacture of pork and for guaranteeing the wholesomeness of the pork as a food would then be placed precisely where that responsibility belongs, namely, upon the manufacturer or packer. The loopholes in such a method of control would be few in-

deed and the protection which would be afforded to the public would be adequate. In short, the pork supply would be safe for human consumption.

We believe that the most practical method of control of trichinosis in the United States is the method of processing all pork. It remains for the public to insist that its health be adequately safeguarded against the danger of acquiring trichinosis in the pork which it consumes. There is no question but that sooner or later the public will demand such protection.

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